American Heart Journal

VOL. 40 SEPTEMBER, 1950 No. 3

Original Communications

MYOCARDIAL INFARCTION SIMULATING ANGINA PECTORIS

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ALTHOUGH the clinical differentiation of angina pectoris and myocardial infarction has been placed on firm grounds,[1] observations recently made encourage the belief that the usual criteria may in some instances lead to an erroneous diagnosis. It has been held basic that in the former, chest pain appears when increased stress is placed upon the cardiac musculature, while in cases of myocardial infarction there is pain in the chest at rest. Other well-known points of difference are the duration and severity of the pain, the presence of fever, leucocytosis, and an elevated sedimentation rate, as well as the therapeutic measures (nitroglycerin, morphine, etc.) for relief. In angina pectoris the electrocardiogram appears normal or may reveal minimal to major aberrations. On the other hand, the progression of the electrocardiographic changes in myocardial infarction is a very important diagnostic consideration.

In patients who have been subjected to attacks of angina pectoris for years, infarction of the myocardium may finally result. In these instances where there is an inadequate collateral circulation, the final obliteration of the lumen of the coronary vessels by atheromatous plaques eventuates in infarction. Infarction will also take place when the occlusive process occurs rapidly and without sufficient time for the anastomotic vessels to function.

The following cases are reported wherein chest pain was present only on exertion (as with angina pectoris), but serial electrocardiograms demonstrated changes consistent with the diagnosis of myocardial infarction. These patients masquerading as victims of angina pectoris already had myocardial necrosis.

CASE REPORTS

CASE I.—L. W., a 58-year-old white woman, in excellent health until two months before her present illness, stated that during this latter interval she noticed the onset of pain radiating across the chest on exertion, lasting a few minutes and subsiding promptly with rest. A week prior to her initial examination she experienced pain more severe and of longer duration while climbing a

Received for publication April 6, 1950.

flight of subway stairs. After a half hour rest, she resumed her usual activities. No other symptoms of diminished cardiac reserve were presented other than some shortness of breath. The past history failed to reveal any blood pressure elevation.

On physical examination no unusual cardiac findings were observed. The heart was not enlarged. The blood pressure was 170/100 mm. Hg. Fluoroscopic studies showed elongation of the aorta.

The electrocardiogram (Fig. 1) was normal except for diphasic T waves in $CF_{4,6}$. The diagnosis of angina pectoris was made and therapy instituted. During the following week the patient was ambulatory and without symptoms. No change in the cardiac findings was noted.

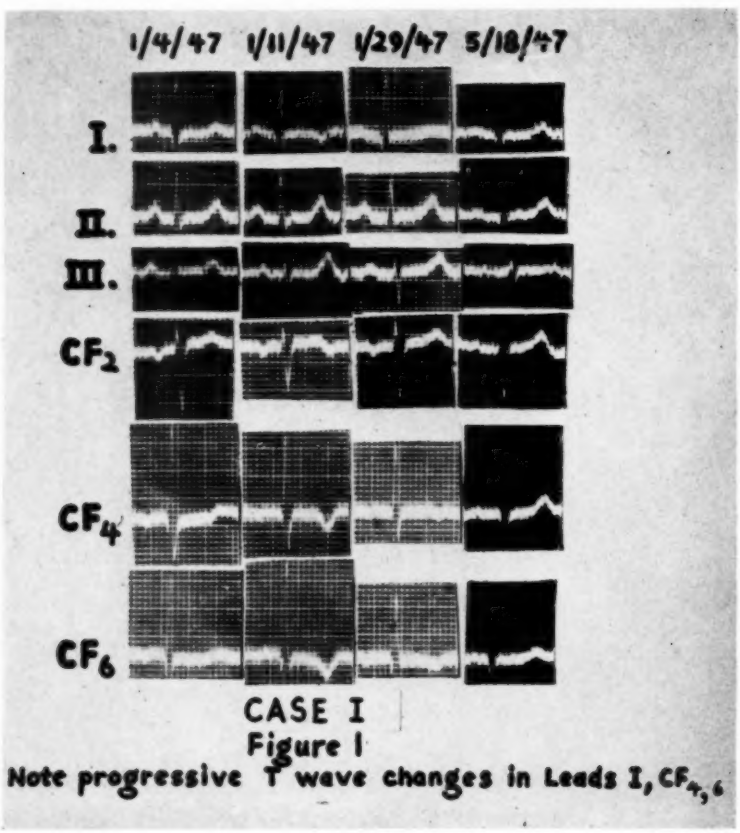

Fig. 1.

The blood pressure at this time was 110/80 mm. Hg. The sedimentation rate was 22 mm. in one hour (normal, 10-15 mm. in one hour). The electrocardiogram now presented T-wave inversions in Leads I, CF_4, and CF_6. She was confined to bed for a five-week period and made an uneventful recovery. At no time was any pain present while she was resting. The electrocardiogram returned to a normal configuration in five months. At present, two years after the onset of her illness, she is well except for occasional anterior chest pain on excitement or moderate exertion. The electrocardiogram has remained normal.

Summary: A 58-year-old woman with a history of angina pectoris presented progressive electrocardiographic findings of myocardial infarction following a prolonged period of pain on climbing a flight of subway stairs.

CASE II.—S. E., 20 years of age, while walking, suffered with severe precordial pressure lasting five minutes. There was an associated "cold sweat." Later on the same day, while playing

ball, he had a recurrence of the same pain. This continued for several days following moderate effort. Pain was never present while he was at rest. Physical examination did not reveal any cardiac pathology. The initial electrocardiogram (Fig. 2)* showed inversion of the T wave in Leads I and $CF_{2,4}$. One week later the same abnormalities were noted. Seven months later the electrocardiogram was normal.

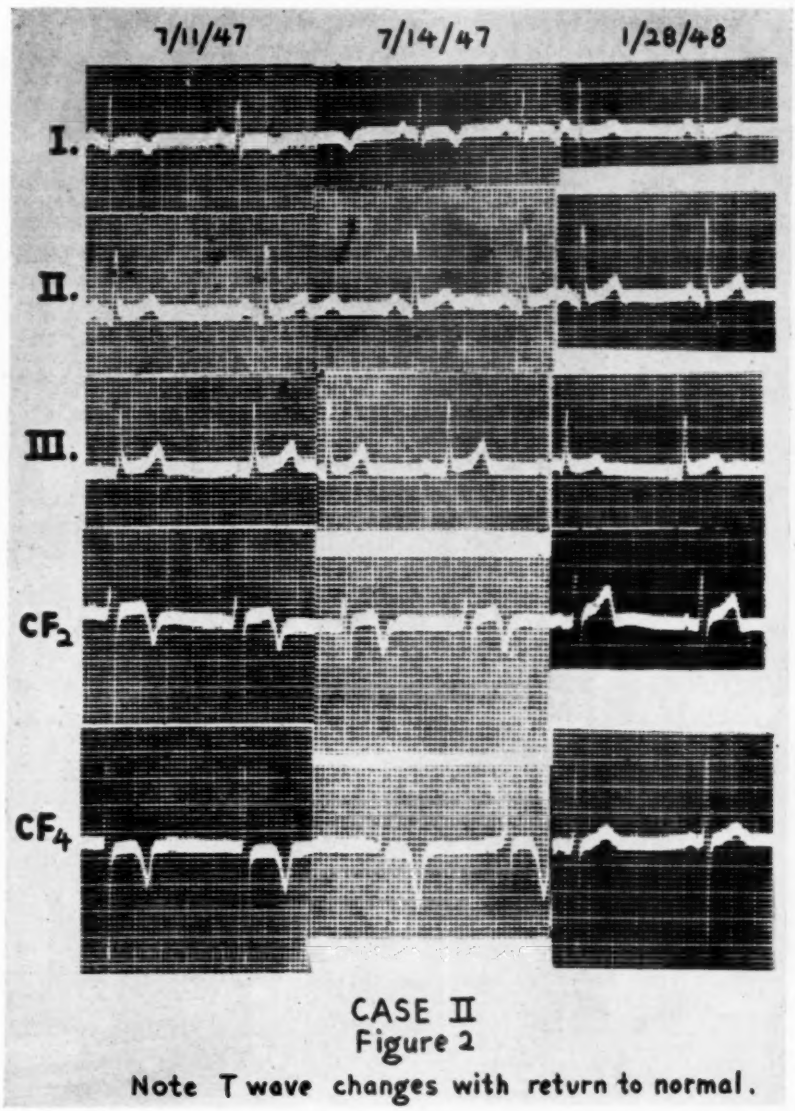

Fig. 2.

Summary: A 20-year-old man had several episodes of severe anterior chest pain associated with a "cold sweat" while exercising. The electrocardiograms indicated an acute myocardial infarction.

*I wish to thank Dr. Reuben Finkelstein for permission to use these electrocardiograms.

CASE III.—S. S., a 52-year-old salesman, had a "pressing" pain in his anterior chest and a "choking" sensation on physical exertion for about three years. A few weeks prior to admission his symptoms appeared after he had walked only two blocks. Blood pressure elevation was present for six months. He had no pain whatever at rest.

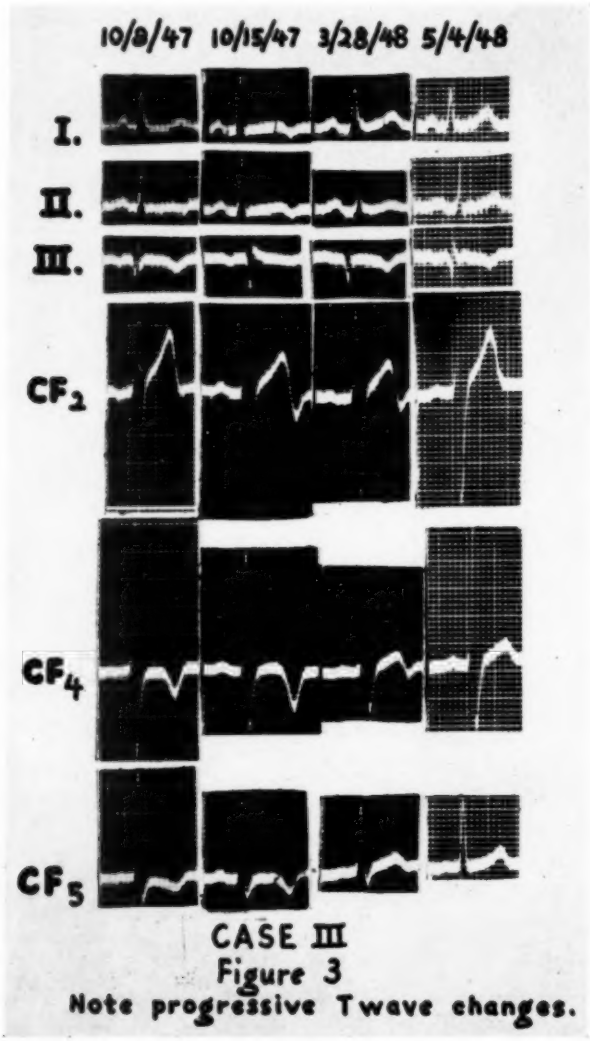

Fig. 3.

On physical examination the findings were essentially as follows: The blood pressure was 170/100 mm. Hg. There was minimal enlargement of the left ventricle, but no congestive phenomena were found. An electrocardiogram (Fig. 3) showed inversion of the T wave in Leads II, III, and $CF_{4,5}$, and a significant Q_3.

Because of the recent acceleration of his symptoms, he was hospitalized. During the three-week period of bed rest he was entirely comfortable; however, the electrocardiograms and sedimentation rate studies (as high as 69 mm. per hour), etc., persisted in following the changing pattern typical of myocardial infarction. After six months the T wave in CF_4 was still inverted. The latter disappeared two months later (Fig. 3).

Summary: A 52-year-old man with a three-year history of angina pectoris was suspected of having myocardial necrosis because of the acceleration of his symptoms. His further course demonstrated a changing electrocardiographic pattern on serial study suggestive of myocardial infarction.

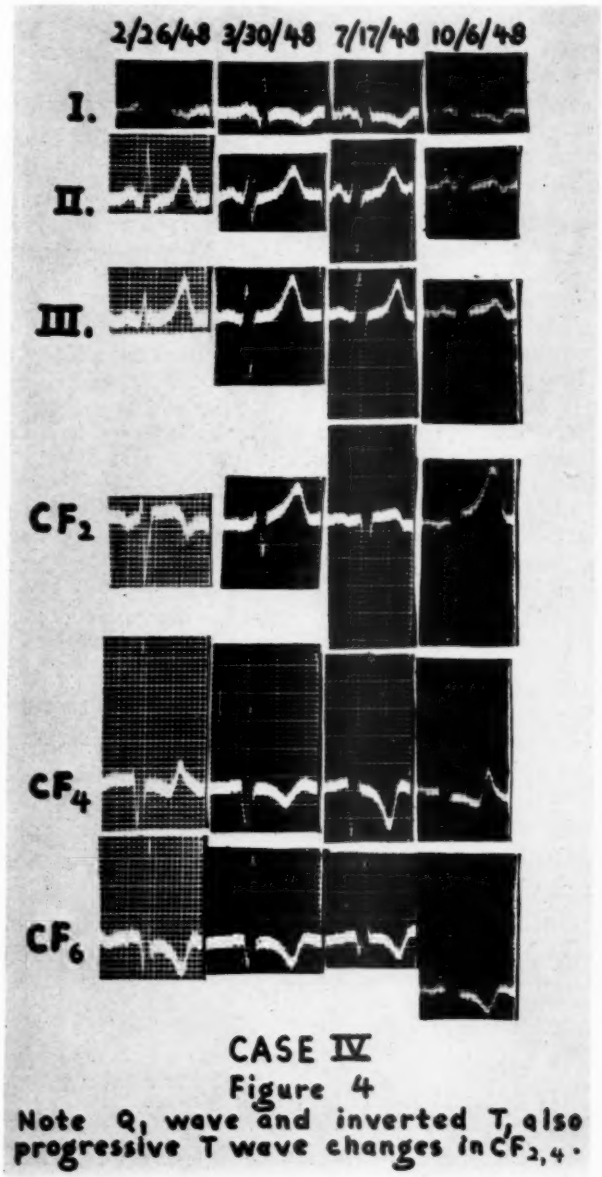

Fig. 4.

CASE IV.—P. L., 39 years of age, complained of substernal pain which appeared on walking and with excitement for a two-year period. In the few weeks prior to examination pain appeared upon less effort. His symptoms were never present while he was resting. There was no hyper-

tension. No abnormal cardiac findings were observed on physical examination. The electrocardiogram (Fig. 4) showed significant Q waves and ST depression in Leads I and $CF_{4,6}$; T waves in Leads I and CF_6 were inverted. During six weeks in bed he remained symptom free, but the electrocardiographic changes were indicative of an anterior wall infarction. Sedimentation rates were as high as 50 mm. per hour. Eight months later, he was back at work, but he is subject to occasional, mild substernal pressure when overactive. The electrocardiogram (Fig. 4) has remained abnormal: T waves in Leads I and $CF_{4,6}$ inverted, large Q waves in Leads I and in $CF_{2,4,6}$.

Summary: A 39-year-old man with angina pectoris for two years presented an acceleration of his symptoms just prior to coming under our observation. The electrocardiograms were indicative of an anterior wall myocardial infarction.

CASE V.—I. G.,* 47 years of age, had a history of hypertension for ten years. Routine electrocardiographic studies four years ago were normal. For four weeks prior to examination he had a substernal "pressing" pain radiating to his throat with an associated pain in his right elbow, which occurred only after he walked three blocks and which was relieved by resting. Pain never appeared at rest, and it never awakened him from sleep. There was no exertional nor nocturnal dyspnea. He was a heavy smoker. His mother had hypertension and diabetes.

The examination revealed the following: The blood pressure was 205/98 mm. Hg. No signs of decompensation were present. The heart was of a hypertensive configuration with enlargement to the left, both on percussion and fluoroscopic examination. A loud, rough systolic murmur was heard over the entire precordium, loudest in mitral and aortic areas. The second aortic sound was accentuated. The electrocardiogram (Fig. 5) showed a low T_1, inversion of $T_{2,3}$, and ST depression in CF_6.

He was confined to bed for two weeks, during which time he was symptom free. Sedimentation rate was 20 mm. in one hour (normal, 18 mm. in one hour).

Since resuming activity he has had minimal substernal pain and numbness in his right arm only after excessive excitement or exertion.

An examination one month after the original showed no changes except that the blood pressure was 170/90 mm. Hg. However, the electrocardiogram revealed progressive changes indicative of an anterior wall infarction (Fig. 5), $T_{1,2}$ inverted, deep Q, elevation and rounding of the ST segment, T-wave inversion in CF_4, and inverted T in CF_6.

Summary: A 47-year-old man with a history of hypertension, a significant family history, and chest pain on effort for four weeks is presented. No pain was ever present at rest. The electrocardiogram revealed the progressive changes consistent with the diagnosis of an anterior wall myocardial infarction.

The following case report has been included in this series on the supposition that when hospitalization was first suggested, impending infarction was suspected. Whether or not myocardial necrosis already had been taking place several days before the fatal outcome can only be conjectured. Similarly, whether or not immediate immobilization at that time would have affected the ultimate course can only be guessed at.

CASE VI.—H. R., a 36-year-old white man, complained for a year of a "burning sensation" in his left chest on moderate activity. This "feeling" occasionally radiated down both his arms and disappeared promptly with rest. He had no other symptoms referable to the cardiovascular system. His systolic blood pressure was at times as high as 160 mm. Hg. He smoked one pack of cigarettes daily.

The family history was significant in that his father had angina pectoris, and a brother had died of "coronary thrombosis" at the age of 32 years. Chest pain commenced soon after his brother's death.

On physical examination his blood pressure was 140/100 mm. Hg. There were no abnormal cardiac findings. Urinalysis, sedimentation rate, and electrocardiographic studies (Fig. 6) before

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*I wish to thank Dr. Joseph Weinstein for permission to include this case report.

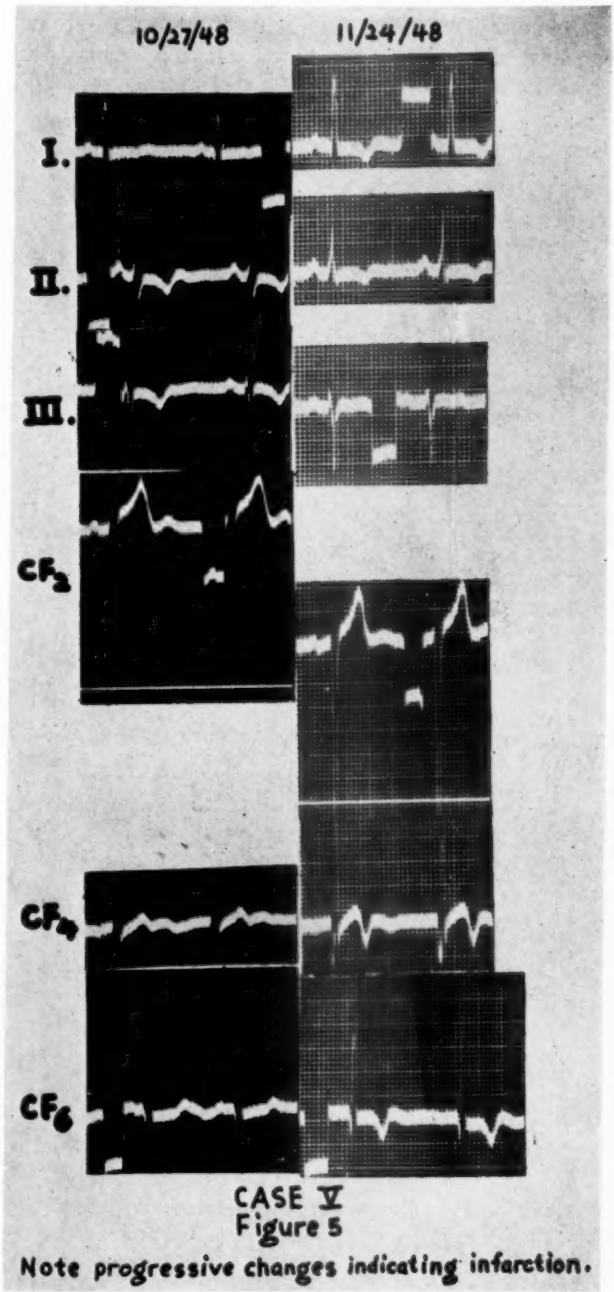

Fig. 5.

and after exercise were normal. He was placed on a regimen of limited activity, smoking was forbidden, and he was instructed to use nitroglycerin whenever necessary.

Ten months later he stated that the pain in his chest still appeared with effort, but the nitroglycerin did not give relief as promptly in the past two weeks as it had before. He had no discomfort while at rest. The physical examination was essentially negative. The electrocardiogram

(Fig. 6) was normal, but after exercise ST_2 was depressed almost 2 mm. He was treated with aminophylline suppositories and nicotinic acid, 100 mg., three times a day. There was no improvement over a two-week period, and hospitalization was recommended. On the following day,

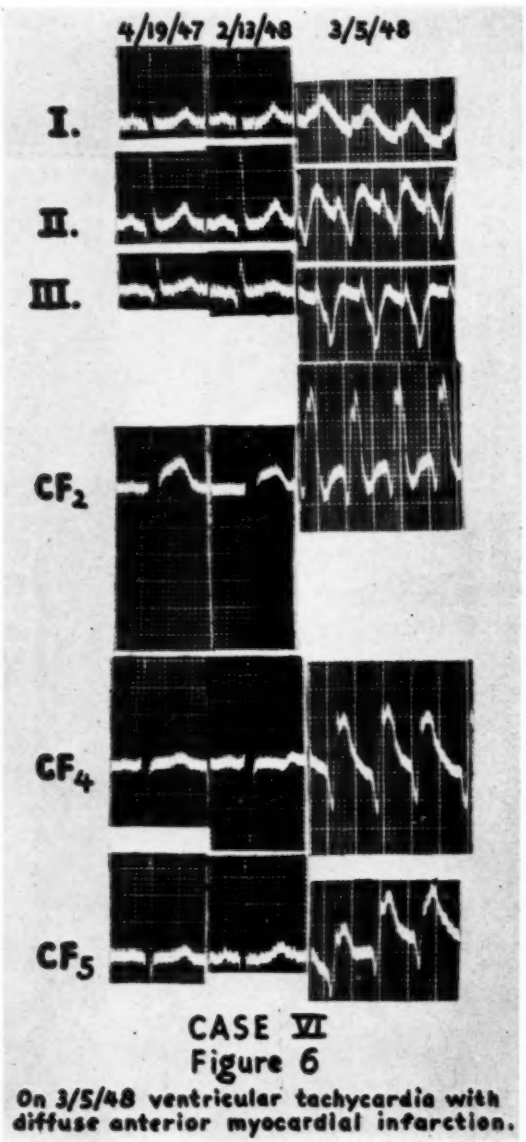

Fig. 6.

while shaving prior to departure for the hospital, he suffered severe anterior chest pain which lasted forty-five minutes. This marked the first appearance of chest pain while at rest. In bed he remained symptom free for twelve hours; chest pain then recurred which was relieved by morphine sulfate, ¼ grain subcutaneously. Two hours later he suddenly went into shock and ceased breathing. An electrocardiogram (Fig. 6) taken just before death revealed a ventricular tachycardia and a diffuse anterior wall myocardial infarction.

Summary: A 36-year-old man with a significant family history of coronary artery disease had angina pectoris for almost two years, starting immediately after a brother died of coronary thrombosis. A myocardial infarction was suspected when nitroglycerin began to lose its previous effectiveness. Pain at rest appeared only terminally. Death was the result of a diffuse myocardial infarction.

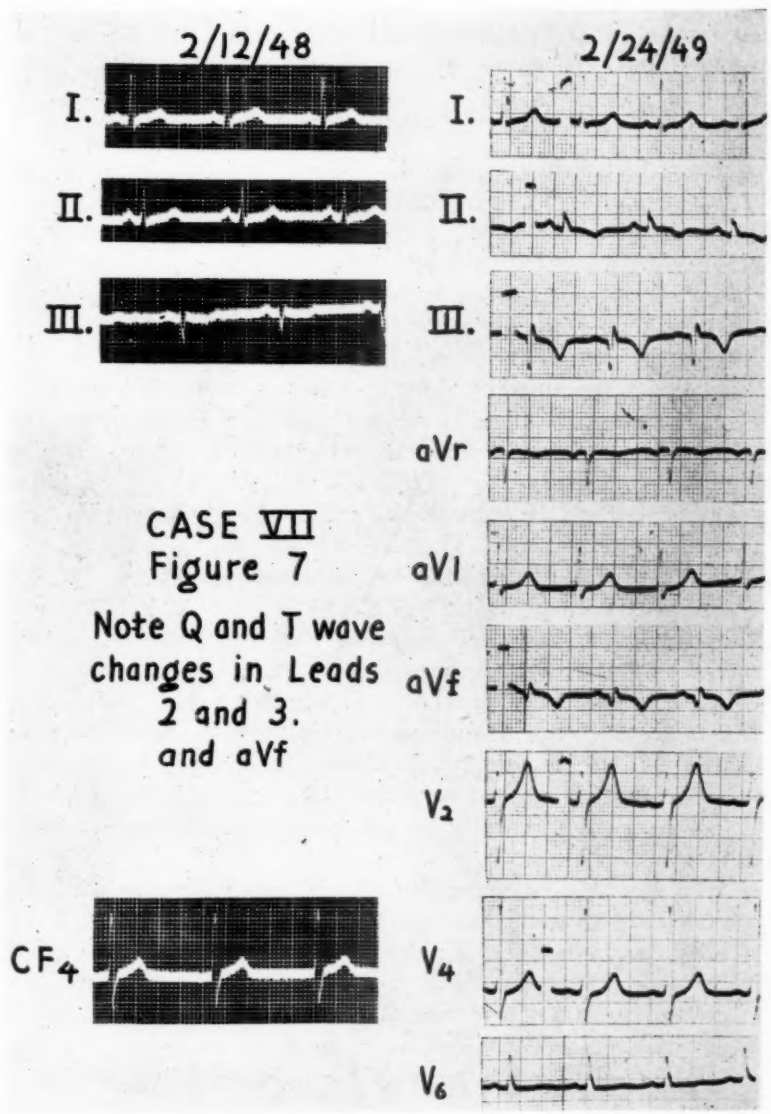

Fig. 7.

CASE VII.—I. F., a 40-year-old white man, felt well until five months previous to examination when he began to have pressing pain in his anterior chest on exertion, relieved by rest within a few minutes. No pain was ever present at rest. He was also short of breath on walking two or three blocks. He had no other symptoms referable to the cardiovascular system. There was no history of rheumatic fever or hypertension. He smoked one pack of cigarettes a day.

Examination revealed an obese man with no evidence of decompensation. The heart was not enlarged; sounds were of good quality; the second aortic sound was greater than that at the pulmonic area; sinus rhythm was regular. The roentgenogram of the heart revealed no enlargement. Sedimentation rate was normal. The electrocardiogram on Feb. 12, 1948, was normal. On Feb. 24, 1949, there was evidence of a posterior wall infarction (Fig. 7).

Summary: A 40-year-old white man is presented with a history of "pressing" anterior chest pain on effort, relieved by rest. No pain was ever present at rest. The electrocardiogram was indicative of a posterior wall infarction.

COMMENT

The common factors in the cases described consisted of pain on effort for a varying period of time with no symptoms at rest and the presence of an electrocardiographic pattern typical of myocardial infarction. The electrocardiographic changes were not those of coronary insufficiency[2] or transient myocardial ischemia. The presence of significant Q waves and the persistence of the abnormalities over several months or longer are not the usual findings of a rapidly passing ischemic lesion of the myocardium. The clinical picture does not resemble the one of "coronary failure" as described by Freedberg and co-workers[3] in which prolonged chest pain and unresponsiveness to nitroglycerin are present, and wherein no objective evidences of myocardial necrosis such as fever, elevated sedimentation rate, and a changing electrocardiographic pattern are found. The patients had pain only on exertion yet demonstrated electrocardiographic findings consistent with myocardial infarction.

The exact nature of the underlying pathology cannot be stated with accuracy because of the absence of autopsies. One of the patients (Case 6) had a massive infarction as the terminal event. Myocardial infarction was diagnosed in the others on the basis of a changing electrocardiographic pattern together with other factors such as the elevated sedimentation rate. The infarction may have been produced by prolonged coronary spasm or by thrombosis within the coronary tree. It is commonly accepted that angina pectoris is the result of paroxysmal, relative, myocardial ischemia.[4] Whether this is due to arterial spasm or to the inability of the sclerotic vessels to dilate during periods of increased work is still unknown.

Those who believe that vasospasm is the underlying mechanism maintain that the effect of nitroglycerin is to relieve the vasospasm, while their opponents insist that this drug merely dilates the more elastic anastomotic vessels. Recent work[5] lends support to the theory of vasospasm. Using ergonovine maleate by the intravenous route, the typical clinical picture of angina pectoris was produced with corresponding electrocardiographic changes characteristic of coronary insufficiency. Relief from the induced pain was obtained with nitroglycerin. The factor of increased work load was not present as only slight or no increases in pulse and blood pressure were noted. In these instances of ergonovine-induced angina, coronary vessel spasm would seem the more rational explanation.

Experimentally[6,7] it has been demonstrated that coronary obstruction for more than twenty minutes will produce irreversible myocardial changes. Blumgart[8] states that in human beings it is probable that anginal attacks not infrequently leave their mark on the myocardium in the form of fibrous scars. This

appears plausible particularly in individuals with advanced coronary artery disease in whom the myocardium may already be in an impoverished state.

The importance of the early recognition of myocardial infarction is that with proper bed rest and sedation the demands on the heart are reduced until such time when the collateral circulation may become established, allowing for the healing of the ischemic portion of the myocardium. It is suggested that further investigation and serial electrocardiographs be made in patients having a history of angina pectoris with the appearance of (a) prolonged pain or (b) pain following less effort or (c) the absence or slowness of relief with nitroglycerin.[9]

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MYOCARDITIS IN POLIOMYELITIS

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THE occurrence of myocarditis during the course of poliomyelitis was not fully appreciated until the report of Saphir and Wile[1] and most recently of Ludden and Edwards.[2] The development of myocarditis in poliomyelitis is now well established. In 1910, Robertson and Chesley[3] reported that in five of six fatal cases of poliomyelitis there was swelling of the myocardial fibers and interstitial edema. Abramson,[4] Landon,[5] Smith,[6] and Cowie and associates[7] subsequently reported on occasional cases of poliomyelitis in which there were myocardial changes. None of these men attached too much significance to the lesion, and they did not regard it as a frequent and integral part of the disease. In 1942, Saphir and Wile[1] reported a significant involvement of the myocardium in six of seven cases at necropsy. Peale and Lucchesi[8] corroborated these findings in five of nine cases. Again, in 1945, Saphir,[9] in reviewing the visceral lesions in poliomyelitis, reported ten cases of myocarditis out of seventeen at necropsy. In these ten cases the hearts were described as being generally dilated, soft, and flabby. The papillary muscles were generally flattened, and the myocardium was gray or brownish-gray and of a boiled appearance. Although microscopically there was no myocardial necrosis, considerable inflammatory changes were present. No endocardial lesions were noted. In three cases the wall of the aorta contained an edema-like material. Saphir attributed the sudden death in one of these cases to the myocarditis. Other visceral changes in this group of cases included: edema, hyperemia, interstitial inflammation of the lungs, and hyperplasia of Peyer's patches, the spleen, and mesenteric lymph nodes. There were no other visceral lesions of significance.

The most comprehensive study on this subject was made recently by Ludden and Edwards.[2] They investigated at necropsy the cases of thirty-five patients who died of poliomyelitis at the Mayo Clinic. These cases were gathered over a twenty-one-year period. In fourteen instances varying degrees of myocarditis were present. Endocardial lesions were also described.

In none of the reports was there any indication as to the percentage of the fatal cases in which a necropsy was performed. It is therefore impossible to arrive at an accurate estimate of the true incidence in all fatal cases. The incidence as noted varied considerably, as did the degree and the characteristics of the histologic involvement. For example, Dolgopol and Cragan[10] found acute

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Received for publication April 19, 1950.

myocarditis present in only sixteen of eighty-seven patients. Their figures, however, varied with the number of sections of myocardium studied.

In a recent outbreak of poliomyelitis occurring in the summer and fall of 1949 in Westchester County, N. Y., there were fifteen fatal cases of poliomyelitis. The total population of this area is approximately 600,000. Eleven of these patients died at Grasslands Hospital, and necropsies were done on nine. In 1947 and 1948, there were, respectively, two and three deaths from poliomyelitis in the entire county. All of these patients died at Grasslands Hospital, and necropsies were done on all. Thus it was possible to study the hearts of fourteen of the sixteen who died. From this group it was thought that we might obtain a fairly representative picture of myocarditis as it occurs in all deaths from poliomyelitis.

In addition to the problem of the incidence and the degree of involvement of the myocardium, other questions remain unsettled. The exact role of the group of poliomyelitis viruses in the production of the myocarditis is unclear. Some believe that the myocarditis is merely a nonspecific manifestation secondary to either toxicity, various forms of medication, anoxia, serum therapy, or pneumonia. Others believe that the myocarditis is a specific consequence of the virus infection. To our knowledge no one has as yet isolated the virus from the myocardium. The clinical significance of the myocarditis is also not too well established. Some believe it is of no import, but others think it may contribute in some degree to the seriousness of the disease. Gefter and associates[11] reported that thirty-two (14.2 per cent) of 226 patients with poliomyelitis had abnormal electrocardiographic tracings. In none of these patients was the myocardium studied at necropsy. Bradford and Anderson[12] reported significant electrocardiographic changes in about 12 per cent of 155 adequately followed cases. Three of four patients who died displayed positive changes. It is hoped that this study of the findings at necropsy of fourteen patients with poliomyelitis may aid in the partial clarification of some of these problems.

MATERIAL AND METHODS

The material was derived from fourteen of sixteen patients who died of poliomyelitis who represented all of the polio deaths at Grasslands Hospital during the years 1947, 1948, and 1949. In 1949, there were, in all, 140 cases of poliomyelitis with a fatality rate of 8.1 per cent. Since myocarditis was anticipated, representative sections of the myocardium were taken from all parts of the heart including auricles, right and left ventricles, interventricular septum, and posterior papillary muscle. All sections were fixed in 10 per cent Formalin and stained with hematoxylin and eosin. Spinal cord and brain were examined in detail in all cases.

Anatomic Observations, Gross.—There was no significant increase in weights of the heart (Table I). In only one case was it possible to observe any gross changes in the heart muscle. This was a 5-year-old boy whose duration of illness was five days. In this instance the myocardium was flabby and pale yellowish-brown. One other patient who had a previous history of chorea and rheumatic fever revealed characteristic rheumatic changes in the mitral valve leaflets and chordae tendineae. This was one of the two patients who did not reveal any

TABLE I. CORRELATION OF AGE, SEX, AND DURATION OF DISEASE WITH HISTOLOGIC FINDINGS

NECROPSY NO.	AGE	SEX	DURATION OF ILLNESS (DAYS)	CLINICAL TYPE	WEIGHT OF HEART (GRAMS)	HISTOLOGIC FINDINGS
133/46	29	M	2	Spinal	350	Edema, fibrin, myocardial necrosis, polymorphonuclears and lymphocytes.
166/46	46	F	22	Bulbar spinal	350	Fibrosis—diffuse and focal. Focal collections of lymphocytes.
118/47	12	F	7	Bulbar spinal	175	Marked infiltration with polymorphonuclears, lymphocytes, and eosinophilic cells. Poor staining of fibers. Edema—nerve lesions.
180/48	14	F	9	Bulbar spinal	200	None.
189/48	34	F	18	Bulbar spinal	325	Fibrosis, moderate, diffuse and focal. Lymphocytes and a few polymorphonuclears, nerve lesion.
133/49	27	F	5	Bulbar	250	Polymorphonuclears, focal eosinophilic cells.
137/49	3	F	6	Bulbar	100	Edema, fibrin, lymphocytes, interrupted fibers, fibrocytes.
143/49	8	F	22	Bulbar spinal	125	Lymphocytes, diffuse, marked. Fibrosis, marked.
138/49	9	F	5	Spinal	150	Edema, fibrin, interrupted fibers. Myocardial necrosis, focal lymphocytes.
183/49	5	M	5	Bulbar	150	Pale myocardium (gross), myocardial necrosis, nerve lesion. Diffuse polymorphonuclears, moderate. Interrupted fibers. Edema.
169 49	26	M	6	Bulbar	350	Fibrin, edema, poor staining lymphocytes. Few polymorphonuclears.
182/49	24	F	43	Spinal	275	None (rheumatic active heart disease).
141/49	30	F	11	Bulbar spinal encephalitic	250	Diffuse—lymphocytes, plasma cells, eosinophilic cells. Rare polymorphonuclears. Fibrosis.
198/49	23	M	9	Bulbar	250	Interrupted fibers, lymphocytes, plasma cells, edema, fibrin. Occasional polymorphonuclear, some fibrosis.

evidence of myocarditis. No other endocardial lesions were noted, and there were no changes in the pericardium.

Histologic Findings.—A composite picture of the myocardium reveals poor staining (with eosin) of the myocardial fibers; separation of these fibers by edema fluid and fibrin, diffuse, focal, and perivascular collections of polymorphonuclear

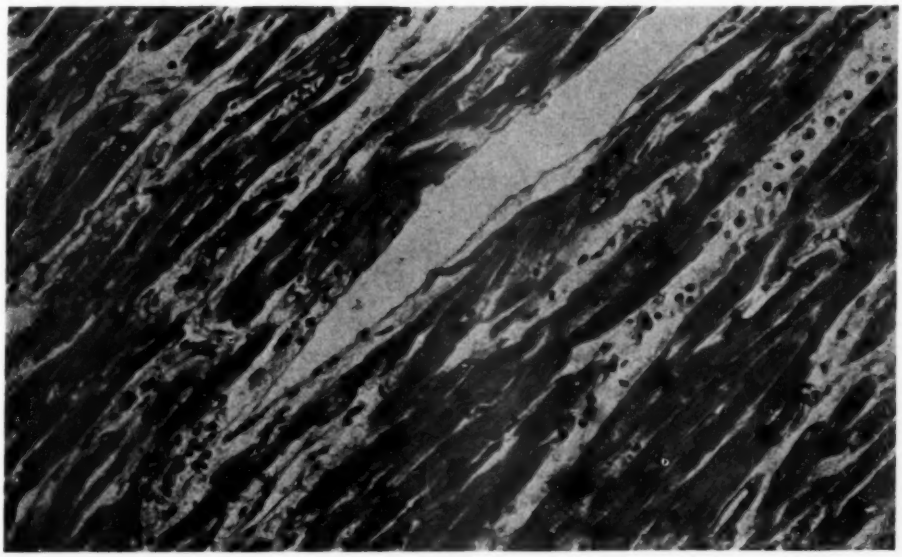

Fig. 1.—Photomicrograph (hematoxylin and eosin stain) of myocardium showing mild polymorphonuclear leucocytic infiltration.

Fig. 2.—Photomicrograph (hematoxylin and eosin stain) of myocardium showing diffuse lymphocytic infiltration.

leucocytes, lymphocytes, occasional plasma cells, and mononuclear cells; hemorrhage; congestion; focal myocardial necrosis with or without cellular infiltration; edema, fibrosis, and cellular infiltration of occasional nerves; and, finally, a diffuse focal or perivascular fibroblastic proliferation (Figs. 1 to 6).

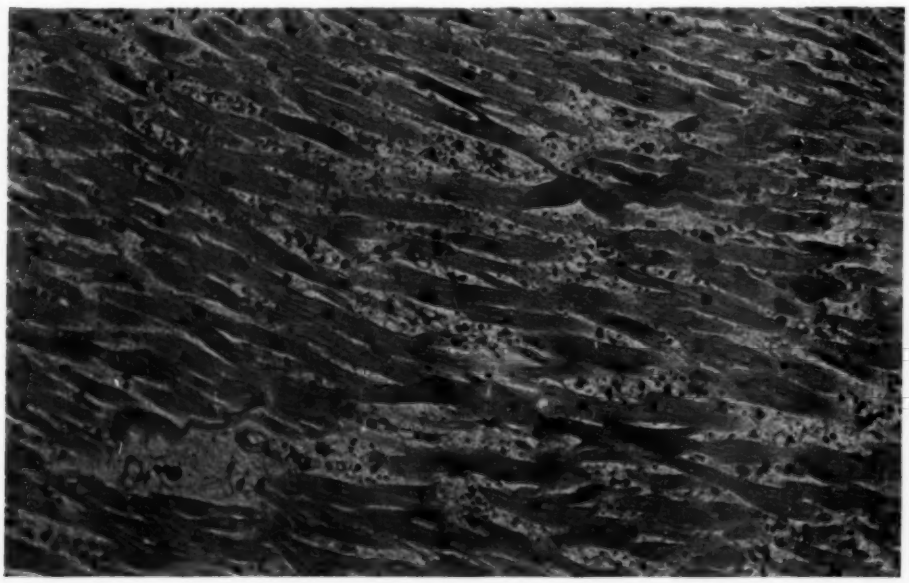

Fig. 3.—Photomicrograph (hematoxylin and eosin stain) of myocardium showing diffuse interstitial hemorrhage.

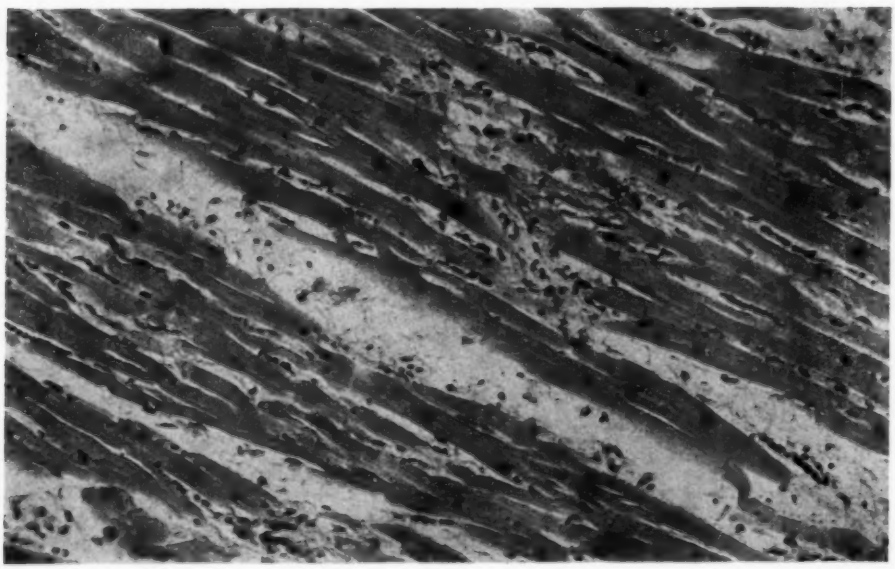

Fig. 4.—Photomicrograph (hematoxylin and eosin stain) of myocardium showing two focal areas of myocardial necrosis.

In twelve of fourteen patients histologic changes of myocarditis were present. The changes varied considerably from one case to another and within the same case from section to section. For this reason accurate grading of the severity of the myocarditis was difficult. With regard for these limitations, four were graded as severe, five as moderate, and three as mild. The endocardium, the valve

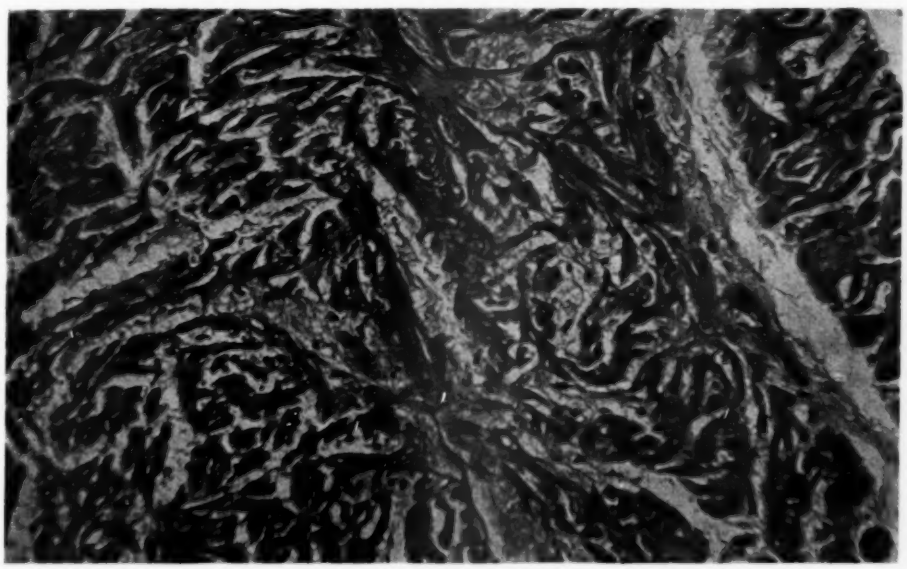

Fig. 5.—Photomicrograph (hematoxylin and eosin stain) of myocardium showing fine interstitial fibrosis.

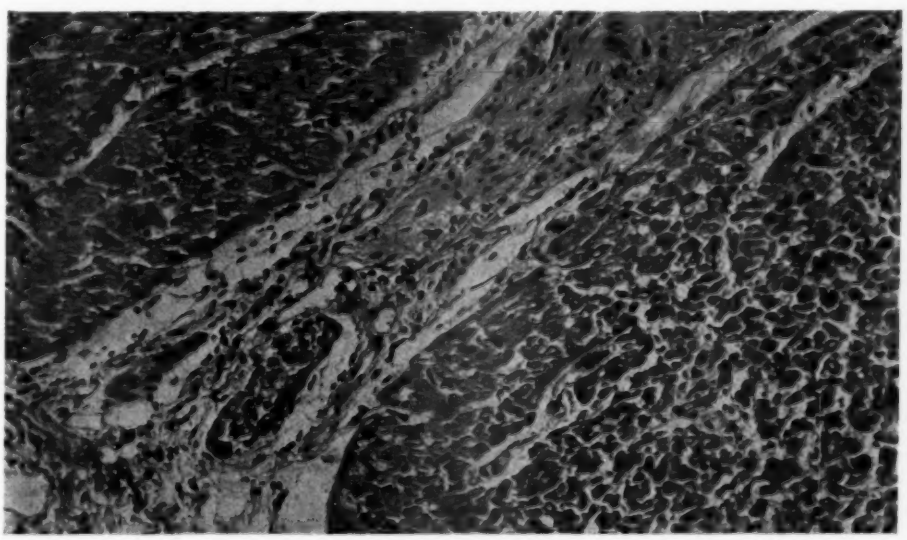

Fig. 6.—Photomicrograph (hematoxylin and eosin stain) of myocardium showing perineural lymphocytic infiltration.

leaflets, the pericardium, and the ascending aorta revealed no significant changes. In all of the patients there were at least some of the characteristic inflammatory and degenerative changes in both the spinal cord and brain. Varying degrees of edema, hemorrhage, congestion, and atelectasis, as well as lobular pneumonia were found in the lungs. The areas of pneumonia, however, were minimal and recent. No inflammatory or degenerative lesions of striated muscles were noted.

The accompanying table attempts to correlate age, sex, duration of illness, clinical type of disease, and weight of the heart, with the histologic changes in the myocardium (Table I).

The duration of illness of those patients that had myocarditis ranged from one case of two days duration to two cases of twenty-two days duration. The one case of two days duration was regarded clinically as a spinal type poliomyelitis. This was a 29-year-old man, who died of extreme ventillatory embarrassment. The myocardium revealed the acute lesion which consisted of interstitial edema, fibrin, focal myocardial necrosis, and focal and diffuse collections of polymorphonuclear leucocytes and lymphocytes. The two cases of twenty-two days duration were an 8-year-old girl and a 46-year-old woman. Both patients were regarded clinically as having bulbar spinal type of poliomyelitis. They both died with marked respiratory difficulty. Their hearts showed essentially similar pictures. Considerable fibrosis was present, and the cellular infiltration consisted predominantly of lymphocytes. These cases illustrate the close correlation of the histologic alterations in the myocardium with the duration of the illness.

Myocarditis was encountered in all clinical types of poliomyelitis. The age of those patients with myocarditis ranged from 3 to 46 years. Ten were female, of whom eight had myocarditis; and four were male, all of whom had myocarditis.

The one patient who revealed obvious gross findings of myocardial involvement was the only patient who during life revealed a finding that might be related to myocarditis. This consisted of a rapid pulse that ranged constantly around 160, despite the fact that the temperature had dropped to near normal. The terminal episode was also suggestive of some degree of cardiac failure. The histologic picture in this case consisted of a marked, diffuse, acute inflammatory cell infiltration that was made up predominantly of polymorphonuclear leucocytes. Numerous focal areas of myocardial necrosis were present as well as occasional nerve lesions.

DISCUSSION

It is realized that usually only the severest cases of poliomyelitis come to post-mortem examination, therefore one cannot make any generalization regarding the myocardium in all cases of poliomyelitis. It was apparent, however, in the examination of the material in this report that myocarditis was almost a constant finding in the fatal cases of poliomyelitis. In contrast to the report of Ludden and Edwards,[2] no significant sex differences were noted. No correlation was noted between the severity of the myocarditis and the age of the patient as they had reported.

The relationship of the virus to the myocarditis, as indicated before, is still unsettled. Only three patients had any significant medication as far as the production of myocarditis is concerned. These three received various forms of sulfonamide therapy. None of the patients received any form of serum therapy. Anoxia as a possible cause for the myocarditis was discounted, since anoxia occurs in a much severer form in other conditions without the development of myocarditis. For instance, in Ayerza's disease where there is intense cyanosis and anoxia, myocarditis is only infrequently noted. Pneumonia which can be the underlying factor in the development of a myocarditis does not produce myocarditis with the frequency seen in poliomyelitis. Even if pneumonia could be considered as a factor it would be extremely remote in this group of cases since pneumonia when present was minimal and terminal.

Helwig and Schmidt[13] have reported the isolation of a virus that produced myocarditis in chimpanzees. The same virus has also been found to be neurotropic by Warren and Smadel.[14] It has produced myocarditis in mice, guinea pigs, and occasionally in rabbits. It has also been stated recently that this is the same virus as the Coxsackie virus discovered by Dalldorf[15] that has produced a clinical picture that mimics poliomyelitis.

For these reasons and because of the close correlation between the histologic picture in the myocardium and the duration of illness, and the presence of focal myocardial necrosis and nerve lesions in the myocardium, it is believed that the etiology of the myocarditis is specifically related to the poliomyelitis group of viruses. It is realized that the virus has never been isolated from the myocardium. Whether serious attempts at such have been made is not known to us. It would be of considerable interest to know what the findings were in the myocardium in experimentally produced poliomyelitis in monkeys, and whether or not attempts at early isolation of the virus from the myocardium have been made.

No instance of endocarditis in poliomyelitis had been reported by Saphir.[9] However, Ludden and Edwards[2] reported two such instances. Although they did not definitely state so, it was implied that the endocarditis might be the direct result of the virus infection. From the description of the endocardial lesions in their patients it would seem more likely that these were instances of nonspecific thromboendocarditis.

It seems that in our group of cases the myocarditis did not play a significant clinical role with the exception of the one patient already described where the pulse rate ranged around 160. Recovered cases of poliomyelitis have to our knowledge shown no evidence of subsequent damage to the myocardium. However, it is clearly apparent that poliomyelitis is a debilitating disease, and it takes many patients, even those with minor paralyses, many weeks and even months to recover fully. The presence of myocarditis in a subclinical phase in these cases may be a factor contributing to the prolonged convalescence and debility.

SUMMARY AND CONCLUSIONS

1. Myocarditis is a frequent finding in deaths from poliomyelitis. It was observed in twelve of fourteen cases at necropsy.

2. The histologic findings correlated closely with the duration of illness.

3. The severity of the myocarditis varied from case to case and within the same patient from one area of the myocardium to another.

4. No significant relationship of the incidence or severity of myocarditis could be correlated with the age, sex, or clinical type of illness.

5. In only one patient could any clinical evidence of myocarditis be found.

6. The relationship of the virus to the development of the myocarditis was discussed, and a specific virus etiology of the myocarditis was favored in this report.

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ACTIVE RHEUMATIC CARDITIS IN PATIENTS OVER 40 YEARS OF AGE

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ACTIVE rheumatic heart disease is primarily a disease of children and young adults. Its presence in patients over 40 years of age is generally unsuspected unless the manifestations are classical. Rheumatic heart disease has frequently been seen at this hospital in patients of the older age groups. The patients are, however, highly selected since they are admitted only after protracted illness in general hospitals. In only a few of these individuals was the diagnosis of rheumatic heart disease entertained prior to their transfer from other hospitals.

Thirty-four cases of histologically active rheumatic heart disease were selected from 1930 autopsy protocols to obtain the material for this report. The clinical records of these patients were studied, and pertinent data were tabulated in an effort to determine whether cardiac activity noted in the histologic sections resulted in clinical manifestations. Furthermore, our clinical pathologic study was undertaken to determine whether patients over 40 years of age, who exhibited histologic evidence of rheumatic carditis on port-mortem examination, differed in their clinical manifestations of activity from patients in the younger age groups.

The standards used for the histologic diagnosis of rheumatic activity were those recently reported by Rosenthal and Feigen,[1] which agree substantially with those set forth by the Committee of the New York Heart Association.[2] Briefly, these consisted of acute and chronic inflammatory involvement of the valves and/or myocardium. The former exhibited acute granulation tissue, including fibrin, inflammatory cells, and newly formed blood vessels. Aschoff bodies were occasionally found in the myocardium, and the degree of inflammatory response varied considerably although the lesions were seen in foci which had previously been the sites of inflammation. The pathognomonic chronic changes consisted of thickened valves, sometimes hyalinized, with a moderate to severe infiltration of lymphocytes, diffusely and focally distributed throughout the cardiac tissue.

The criteria for the clinical diagnosis of active rheumatic heart disease in children and young adults are well known.[2] Rosenberg,[3] after studying the clinical aspects of rheumatic fever in 1,000 U. S. Navy personnel, concluded that only in a typical case with migratory polyarthritis, carditis, electrocardiographic abnormalities, leucocytosis, and increased sedimentation rate could the diagnosis of rheumatic activity be made without equivocation. However, many patients,

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Received for publication June 2, 1950.
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especially those older than 40 years of age, do not present this combination of findings, and in these the diagnosis is likely to be difficult.

A survey of the literature for the past ten years reveals few reports dealing with rheumatic carditis in the older age groups. Greene and Bennett[4] reported one case of active rheumatic heart disease in a patient 64 years of age, and it was their belief that active rheumatic heart disease was rare after the fifth decade. Rothschild, Kugel, and Gross[5] noted histologic activity only twice in the sixth decade and once in the seventh decade in 161 cases of chronic rheumatic heart disease. Rakov and Taylor[6] reported one instance of active carditis in an elderly individual. DeGraff, Lingg, and Cohn,[7] reviewing over 1,000 patients with rheumatic heart disease of whom 644 were examined post mortem, came to the following conclusions: the average age of initial infection was 17 years; the average age of the first signs of cardiac insufficiency was 28 years; and the average age at death was 33 years. These findings are valid for the group studied and include the majority of patients with rheumatic heart disease. In general, then, it has been clinically accepted that most patients with rheumatic fever die young and that activity is confined to children and young adults and rarely involves the hearts of patients over 40 years of age.

Juca and White[8] studied 100 unselected necropsy records from patients with rheumatic heart disease to determine the cause of death. Since this material was unselected, two important facts emerge from their study: 57 per cent of the patients between 20 and 89 years of age at the time of death were over 40 years of age, and the oldest was 89. Of the patients over 40 years of age, 19 per cent exhibited histologic findings significant of rheumatic activity at the time of death. Kerr[9] also has observed that many patients with chronic rheumatic heart disease exhibit the histologic evidence of rheumatic activity at necropsy.

Representing another viewpoint, Roth[10] believes that adult rheumatic fever has its smoldering stages, a fact which has impressed him more and more in recent years. Patients who have died from what was believed to be chronic heart failure and without any clinical evidence of rheumatic activity, have been proved at autopsy to have active carditis. Others in whom cardiac involvement was not suspected but who were believed to have had auricular fibrillation associated with arteriosclerotic heart disease have been found by Roth to have active smoldering rheumatic carditis at autopsy. Recently, Rogers and Robbins[11] reported their observations on latent rheumatic myocarditis. Their series included 41 patients; eighteen were over 40 years of age. All of these patients had active carditis histologically, but rheumatic carditis was recognized clinically in only eight.

ANALYSIS OF THE DATA

The records of thirty-four patients were studied (Table I). Six were in the fourth decade, fourteen in the fifth, eight in the sixth, three in the seventh, two in the eighth, and one in the ninth decade. There were nineteen men and fifteen women. Of these, twenty-eight were white, and six were Negro. Nine patients had clinical and pathologic evidence of rheumatoid arthritis of the peripheral joints. Prior to death the final clinical diagnosis usually was arteriosclerotic

TABLE I

PATIENT NO.	AGE AND SEX	TEMPERATURE* (°F.)	PULSE PER MIN.	X-RAY FINDINGS†	ECG‡
1	70 M	98.0- 99.6	75- 85	Hypertensive-shaped heart.	Prolonged P-R interval.
2	54 M	100.0-102.0	90-130	Normal heart.	Left ventricular preponderance; abnormal P_2; prolonged Q-T interval; LAD.
3	43 F	99.0-100.5	80-100	Mitral-shaped, enlarged heart; accentuated pulmonary artery.	Abnormal P waves in all leads; prolonged Q-T interval; RAD.
4	42 F	99.0-101.8	75-110	Generalized enlargement of the heart.	A.F.; prolonged Q-T interval; RAD.
5	57 F	99.4-101.2	65- 80	Mitral-shaped, enlarged heart; pulmonary congestion.	A.F.; RAD.
6	48 M	99.0-101.0	75- 90	Heart enlarged in all diameters; mitral and aortic-shaped heart.	A.F.
7	54 F	98.6-100.0	70- 90	Heart generally enlarged but not typically of hypertensive or aortic heart shape.	Abnormal P waves in all leads; prolonged P-R interval; LAD.
8	54 F	98.0- 99.0	70- 85	Enlarged, triangular-shaped heart; enlarged left auricle and pulmonary artery.	Abnormal P waves in all limb leads; prolonged P-R interval; LAD.
9	66 M	99.0-100.0	75- 90	None recorded.	None recorded.
10	53 M	100.0-101.4	70- 90	Markedly enlarged, mitral-shaped heart.	Abnormal P waves in all leads; prolonged P-R and Q-T intervals; RAD.
11	53 M	99.4-100.0	80- 90	Enlarged mitral and aortic-shaped heart.	A.F.; RAD; digitalis effect.
12	59 F	99.6-101.0	85-110	None recorded.	Prolonged Q-T interval; LAD; left ventricular preponderance.
13	62 F	99.0-100.0	85- 95	None recorded.	A.F.; LAD; digitalis effect.
14	67 F	98.0- 99.0	70- 90	None recorded.	PVCs.
15	89 F	99.0-100.0	70- 90	Heart normal in size and shape.	Abnormal P waves in all leads; LAD; digitalis effect.
16	63 F	98.0- 99.0	70- 80	Heart slightly enlarged generally.	A.F.; LAD; digitalis effect.
17	58 M	99.0-100.0	70- 80	Enlarged heart; enlarged left auricle.	A.F.; prolonged Q-T interval; RAD; PVCs.
18	60 M	99.0-101.0	70-100	Diffuse generalized enlargement; left auricular enlargement; dilated aorta.	Prolonged P-R and Q-T intervals.
19	91 M	99.0-101.0	75-105	None recorded.	None recorded.
20	66 F	99.0-100.0	80- 90	None recorded.	None recorded.
21	78 M	99.0-100.0	40- 60	Generalized heart enlargement of the aortic type.	A.F.; LAD.
22	88 F	98.0- 99.0	50- 60	Mitral-shaped heart with pericardial effusion.	A.F.; low voltage in limb and precordial leads; PVCs.
23	58 F	99.0-102.0	80- 90	Hypertensive type; cardiac enlargement.	None recorded.
24	69 F	99.0-102.0	90-110	Normal cardiac shadow.	PVCs.
25	42 M	99.0-101.0	80-110	Normal cardiac shadow.	Abnormal P_2.

(Table continued on next page)

TABLE I—CONT'D

PATIENT NO.	AGE AND SEX	TEMPERATURE* (°F.)	PULSE PER MIN.	X-RAY FINDINGS†	ECG‡
26	57 M	99.0- 99.6	90-100	Generalized cardiac enlargement with accentuation of middle cardiac segment.	Abnormal P_2; RAD.
27	61 F	99.0-100.0	70- 50	Left ventricular enlargement.	Prolonged Q-T interval; LAD.
28	48 M	99.0-101.2	80-100	Mitral-shaped heart enlargement.	Prolonged P-R interval; right bundle branch block.
29	58 M	99.0-100.0	80- 90	Generalized cardiac enlargement.	Abnormal P waves; left ventricular preponderance.
30	62 M	98.0-100.0	75- 90	Combined aortic and mitral-shaped cardiac enlargement.	Abnormal P waves; left ventricular preponderance.
31	43 M	98.6-100.4	70- 90	Generalized enlargement with mitral - shaped heart; left and right auricular enlargement.	A.F.; bigeminal rhythm; digitalis toxicity.
32	54 M	98.0- 98.6	65- 90	Normal cardiac shadow.	Normal tracing.
33	72 M	98.0- 99.0	75- 95	Hypertensive-shaped cardiac enlargement.	Prolonged P-R and Q-T interval; LAD.
34	52 M	100.0-103.0	80- 95	Normal cardiac shadow.	Normal tracing.

*Oral temperature.
†The terminology is that employed by the Department of Radiology.
‡LAD = left axis deviation; RAD = right axis deviation; A.F. = auricular fibrillation; PVCs = premature ventricular contractions.

and/or hypertensive heart disease, probably because of the age groups concerned. Positive blood serology suggested the diagnosis of syphilitic heart disease in at least one case. The possibility of rheumatic heart disease was entertained at one time or another during hospitalization in twelve of the thirty-four cases, while activity of the rheumatic process was suspected in seven of these twelve cases. Evidently for one reason or another many of these clinical impressions were not sustained (Table II).

A past history of rheumatic fever or rheumatic-like illness was obtained from fourteen patients; one patient had scarlet fever in addition as a child; two patients were comatose on admission, and no history was available. An unsatisfactory history was recorded on one chart. Seven patients gave a history of no past rheumatic manifestations. The physical findings alone suggested heart disease in twenty-seven cases. In seven, evidence of heart disease was not noted on physical examination. Thrills were noted infrequently. Five patients had aortic diastolic and systolic murmurs, while six additional patients had a systolic aortic murmur alone. In thirteen patients, systolic and diastolic apical murmurs were heard, while in eleven additional patients nine had one or both murmurs at both apical and aortic areas. In one patient a friction rub was heard. Murmurs were not heard in nine of the patients, but in one of these the heart sounds were of poor quality. Systolic hypertension was present in fifteen, while diastolic hypertension was recorded in ten individuals.

Laboratory Studies.—The sedimentation rate was elevated in sixteen cases, and in one case it was normal. No sedimentation rate was noted in the records of seventeen patients. Only six patients exhibited polymorphonuclear leucocytosis. A positive serologic test for syphilis was obtained in four patients, but in none was there any evidence of cardiovascular syphilis at autopsy. An anemia was noted in one patient. The rest of the laboratory studies were of no significance.

X-rays, electrocardiograms, as well as temperature curves have been summarized (Table I). Of significance was the fact that in this entire group only two electrocardiograms were considered to be normal, and in these two individuals (Cases 32, 34) the x-ray reports indicated a normal heart. Post-mortem examination (Table II) revealed both of these hearts to be involved by an active rheumatic process. In only a few of these patients were the temperature curves consistently normal. The pulse range of these patients yielded no significant information.

Twenty-two patients received digitalis, and of these, four were inadequately digitalized or died before complete digitalization was effected. Of the eighteen patients adequately digitalized, five became toxic with abnormalities of conduction or rhythm. One patient who had auricular fibrillation maintained a rapid ventricular rate, and in two other patients cardiac failure persisted for many months in spite of adequate digitalis administration. In nine out of twenty-one individuals toxic manifestations due to digitalis administration were thought to be an indication of activity as well as diminished therapeutic response.

DISCUSSION

Rheumatic activity is a clinical term rather than a pathologic one, but it is also true that evidence of clinical activity frequently can be affirmed histologically. However, the point at which clinical activity ceases is not one that can be precisely ascertained histologically. As a matter of fact, it was surprising to note the degree of histologic activity in some of the hearts as compared with the meager clinical manifestations ante mortem. From the study of our cases, all of which showed some histologic evidence of active rheumatic carditis, three groups of patients were classified because of varying clinical expressions of rheumatic activity. In one group, obvious signs of rheumatic activity were present; a second group exhibited adequate clinical manifestations of activity for diagnosis; and in a third group, few or no signs of clinical activity were apparent. Representative cases of each group are listed at the close of the paper to illustrate this division. Of the thirty-two cases in which complete clinical data were available to study activity, ten patients exhibited classical or obvious signs of clinical activity; sixteen patients exhibited adequate evidence of clinical activity; and in six patients minimal or no manifestations of clinical activity were apparent. It appears probable that if the diagnosis of active rheumatic carditis had been considered seriously in spite of the ages of the patients, a correct diagnosis could have been arrived at in most of the patients of the first two groups. As for the third group, the difficulty in making a positive diagnosis represents the same problem encountered in the younger age groups.

TABLE II. COMPARISON OF FINAL CLINICAL IMPRESSION AND AUTOPSY FINDINGS

CASE NO.	ANATOMICAL DIAGNOSIS	CLINICAL DIAGNOSIS
1	Active rheumatic mitral valvulitis; cardiac hypertrophy; sclerosis of the coronary arteries; chronic passive congestion of the viscera.	Hypertensive and arteriosclerotic heart disease.
2	Active rheumatic mitral and aortic valvulitis; active rheumatic myocarditis.	Central nervous system disease, etiology undetermined.
3	Active rheumatic mitral valvulitis; subacute rheumatic myocarditis; myocardial fibrosis and hypertrophy; sclerosis of the coronary arteries; chronic passive congestion; lipoid pneumonia.	Hypertensive cardiovascular disease; cerebrovascular accident; active rheumatic heart disease; lipoid pneumonia.
4	Acute and chronic rheumatic pancarditis; cardiac cirrhosis; infarction of the spleen.	Active rheumatic heart disease; cardiac cirrhosis; anemia, hypochromic, normocytic.
5	Acute and chronic rheumatic pancarditis; mitral stenosis with calcification; cardiac hypertrophy.	Hypertensive and rheumatic (inactive) heart disease; ? rheumatic activity.
6	Acute and chronic rheumatic pancarditis; mitral stenosis; myocardial hypertrophy.	Rheumatic fever and active rheumatic heart disease; ? mitral stenosis.
7	Acute and chronic rheumatic mitral valvulitis; myocardial hypertrophy and fibrosis; active rheumatic myocarditis; sclerosis of the coronary arteries; lipoid pneumonia.	Hypertensive cardiovascular disease; multiple cerebrovascular accidents; pseudobulbar palsy.
8	Acute and chronic rheumatic pancarditis; rheumatoid arthritis.	Hypertensive cardiovascular disease; rheumatoid arthritis; ? inactive rheumatic heart disease.
9	Active rheumatic mitral and aortic valvulitis; acute rheumatic myocarditis; cardiac hypertrophy and dilatation; rheumatoid arthritis.	Arteriosclerotic heart disease; carotid-sinus sensitivity; rheumatoid arthritis.
10	Acute and chronic rheumatic pancarditis.	Active rheumatic heart disease with mitral stenosis and insufficiency.
11	Acute and chronic rheumatic pancarditis; myocardial hypertrophy.	Active rheumatic heart disease with mitral stenosis and tricuspid insufficiency.
12	Acute rheumatic mitral valvulitis and myocarditis; cardiac hypertrophy; nephrosclerosis.	Hypertensive and arteriosclerotic cardiovascular disease; uremia.
13	Acute rheumatic mitral valvulitis; mitral stenosis; cardiac dilatation.	Arteriosclerotic heart disease; biliary calculi.
14	Acute rheumatic pericarditis; active rheumatic myocarditis; myocardial fibrosis; sclerosis of the coronary arteries; rheumatoid arthritis; chronic cholecystitis.	Arteriosclerotic heart disease; rheumatoid arthritis; chronic cholecystitis.
15	Acute and chronic rheumatic mitral and aortic valvulitis; chronic myocarditis, rheumatic type; myocardial hypertrophy; rheumatoid arthritis.	Arteriosclerotic heart disease; rheumatoid and osteoarthritis.
16	Active rheumatic mitral valvulitis and myocarditis; mitral stenosis; cardiac dilatation.	Arteriosclerotic heart disease; acute pharyngitis, *Streptococcus hemolyticus*.
17	Acute and chronic rheumatic pancarditis; cardiac cirrhosis.	Rheumatic heart disease, inactive.
18	Active rheumatic aortic valvulitis; active rheumatic myocarditis; cardiac hypertrophy and dilatation; cardiac cirrhosis.	Syphilitic and hypertensive cardiovascular disease.
19	Active rheumatic mitral valvulitis and auriculitis.	Arteriosclerotic heart disease.
20	Active rheumatic mitral valvulitis; acute and chronic rheumatic pericarditis; rheumatoid arthritis.	Rheumatoid arthritis.

TABLE II—CONT'D

CASE NO.	ANATOMICAL DIAGNOSIS	CLINICAL DIAGNOSIS
21	Subacute rheumatic mitral and aortic valvulitis; acute rheumatic arteritis coronary arteries; myocardial hypertrophy and fibrosis.	Arteriosclerotic heart disease.
22	Generalized arteriosclerosis with moderate coronary sclerosis; active rheumatic auriculitis and myocarditis; mitral stenosis; cardiac dilatation.	Arteriosclerotic heart disease; bronchopneumonia.
23	Active rheumatic pericarditis; acute and chronic rheumatic myocarditis; chronic rheumatic tricuspid and mitral valvulitis; rheumatoid arthritis.	Arteriosclerotic heart disease; rheumatoid arthritis.
24	Acute rheumatic mitral valvulitis; mitral stenosis; rheumatoid arthritis.	Hypertensive and arteriosclerotic cardiovascular disease.
25	Acute rheumatic pancarditis; rheumatoid arthritis.	Rheumatoid arthritis.
26	Acute rheumatic mitral and aortic valvulitis; pulmonary emphysema and fibrosis; cardiac hypertrophy and dilatation.	Chronic nontuberculous pulmonary disease; cor pulmonale.
27	Generalized arteriosclerosis; acute rheumatic mitral valvulitis; meningioma.	Meningioma; generalized arteriosclerosis.
28	Acute and chronic rheumatic pancarditis; myocardial hypertrophy.	Rheumatic heart disease, active; mitral insufficiency; mitral stenosis; aortic insufficiency.
29	Acute and chronic rheumatic mitral and aortic valvulitis; myocardial hypertrophy and fibrosis; coronary sclerosis.	Arteriosclerotic heart disease.
30	Acute and chronic rheumatic pancarditis; acute rheumatic arteritis, pulmonary artery and aorta; mitral and aortic stenosis and insufficiency; hypertrophy and dilatation of the heart; rheumatic pneumonia; infarction of lung.	Arteriosclerotic heart disease; ? inactive rheumatic heart disease; bronchopneumonia.
31	Rheumatic heart disease with aortic, mitral, and tricuspid insufficiency and stenosis; active rheumatic auriculitis, left; active rheumatic myocarditis; cardiac dilatation and hypertrophy; rheumatic arteritis, pulmonary artery; rheumatic pneumonia.	Rheumatic heart disease, inactive.
32	Acute rheumatic myocarditis; subacute multiple sclerosis.	Multiple sclerosis.
33	Chronic rheumatic mitral and aortic valvulitis with insufficiency and stenosis; pericardial effusion; cardiac hypertrophy and dilatation.	Arteriosclerotic heart disease.
34	Acute rheumatic mitral valvulitis and auriculitis; rheumatoid arthritis.	Inactive rheumatic heart disease; rheumatoid arthritis.

It is evident that rheumatic heart disease is occasionally seen at this hospital in patients over the age of 40 years, and that smoldering clinical activity is by no means rare. Only when clinical activity was indicated by classical clinical signs was a correct diagnosis invariably made. Finally, there were certain patients in this older age group in whom clinical evidence for rheumatic activity could not be found, but who nevertheless exhibited the characteristic cardiac findings of activity at necropsy. At the present time we do not know of any method that will aid in the detection of an active rheumatic process in this group prior to necropsy.

CASE REPORTS

Group I.—Clear-cut rheumatic history and findings of rheumatic heart disease.

CASE 10.—This 53-year-old white man had polyarthritis at the ages of 19 and 29 years and symptoms of cardiac insufficiency for three years prior to admission to this hospital. Findings on admission were an enlarged heart including x-ray evidence of an enlarged left auricle, double mitral murmurs, and enlarged liver and peripheral edema. His course was characterized by persistent failure, fever of 99.6 to 101° F., an abnormal electrocardiogram, and toxic responses to digitalis. Post-mortem examination revealed acute rheumatic pericarditis, endocarditis, and mitral and tricuspid valvulitis.

CASE 17.—This 58-year-old white man had rheumatic fever at 10 and 18 years of age and symptoms of cardiac insufficiency four years prior to admission to this hospital. The physical findings included enlarged heart with double mitral murmurs, accentuated pulmonic second sound, and multiple premature contractions. The heart, including the left auricle, was enlarged by x-ray examination. His course was characterized by persistent failure, fever of 99.8 to 101° F., an abnormal electrocardiogram, and poor response to digitalis. Post-mortem examination revealed acute rheumatic tricuspid, aortic, and mitral valvulitis, endocarditis of the left auricle, and arteritis of the aorta and pulmonary arteries.

Group II.—Sufficient rheumatic history and clinical findings indicative of rheumatic heart disease.

CASE 21.—This 78-year-old white man had no past rheumatic history; symptoms of cardiac insufficiency existed for one year prior to admission to this hospital. Findings on admission included double mitral and aortic murmurs and an enlarged heart by physical and x-ray examination. His course was characterized by persistent failure, fever of 99 to 100.6°F., an abnormal electrocardiogram, and toxic responses to digitalis. Post-mortem examination revealed acute rheumatic mitral, and aortic valvulitis and myocarditis.

CASE 16.—This 57-year-old white man had no rheumatic history; symptoms of cardiac insufficiency existed for two years prior to admission to this hospital. Pertinent findings included a systolic apical murmur and an enlarged heart by physical and x-ray examination. His course was characterized by persistent failure, fever of 99.6 to 100.4° F., an abnormal electrocardiogram, and poor response to digitalis. Post-mortem examination revealed acute carditis with Aschoff nodules in the myocardium.

Group III.—Insufficient history or clinical findings to indicate rheumatic heart disease.

CASE 1.—This 70-year-old Negro man had no rheumatic history; symptoms of cardiac insufficiency existed for one year prior to hospitalization. Pertinent findings included hypertension (170/100 mm. Hg), apical and basal systolic murmurs, an enlarged heart by physical and x-ray examination, and an electrocardiographic pattern of left ventricular preponderance. His course was characterized by persistent failure, normal temperature, and questionable toxic responses to digitalis. Post-mortem examination revealed acute rheumatic mitral valvulitis.

CASE 12.—This 59-year-old woman had no past rheumatic history; symptoms of cardiac insufficiency existed for one year prior to hospitalization. The pertinent findings included an apical systolic murmur, hypertension (190/100 mm. Hg), and a heart of normal size on teleoroentgenogram. Her course was characterized by persistent failure, normal temperature (98.6 to 99.6° F.), and poor response to digitalis. Post-mortem examination revealed acute rheumatic mitral valvulitis and active rheumatic myocarditis.

SUMMARY

1. Thirty-four case records of histologically active rheumatic heart disease in patients over 40 years of age were studied.

2. The histologic manifestations of rheumatic activity in these patients were compared with the clinical histories. Contrary to our expectations, this

study did not result in a good clinicopathologic correlation (Table II). Only in our arbitrary Group I was clinicohistologic correlation satisfactory.

3. Three groups of patients have been described as to their clinical manifestations. In general, their counterpart can be found in the younger age groups.

4. It is suggested that the occurrence of active rheumatic carditis in older patients should be considered more frequently so that the clinical diagnosis will be made more often. Unexplained fever and unusual responses to digitalis may be clues to this end.

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SPONTANEOUS RUPTURE OF PAPILLARY MUSCLE OF THE LEFT VENTRICLE

A Clinical Syndrome

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THE rupture of a papillary muscle in the heart has long been recognized by pathologists, but it has defied clinical recognition until recently.[1] Davison,[2] in a review of the subject in 1948, stated that only twenty-eight cases had been reported to that date with none recognized during life. In one of his cases, the diagnosis was suggested for the first time. It is the purpose of this paper to present a clinical syndrome which should suggest this diagnosis correctly in a high percentage of cases and to present a case in which such a diagnosis was made correctly ante mortem.

The recognition of any clinical entity depends to a great extent on two factors: First, it must present specific signs and symptoms which when regarded with the clinical history make the diagnosis probable; and second, the condition must occur frequently enough to make the observer consider it as a probability. After a review of the clinical features of the reported cases in the literature, it has become evident that a clinical syndrome does develop, and that in spite of the relative rarity of the condition clinical recognition may be possible.

CASE REPORT

E. D., a 53-year-old white man, was admitted to the Crile Veterans Administration Hospital, Cleveland, Ohio, on Oct. 24, 1949, complaining of cough, shortness of breath, and bloody expectoration of nine days duration. On October 15, immediately following the drinking of an ounce of bonded whisky, he noted the onset of a dry cough associated with pain in the throat radiating into the epigastrium. The sputum soon became blood-streaked. He went to bed but was awakened during the night with severe shortness of breath. These symptoms persisted until his admission to the hospital. On October 17 he was seen by a physician, a chest film was made, and he was treated with penicillin. The chest film was said to show bilateral pulmonary infiltration of a marked degree. Past history revealed that five days prior to the onset of the present illness he had had a transitory episode of a dull aching pain in the epigastrium, which he had described as "gas pain" and which seemed "to work itself up into the throat." It was not accompanied by dyspnea or signs of shock. In addition, the past history revealed that as a young child he had had inflammation and swelling of the joints of the knees and wrists.

Physical Examination: His temperature was 100° F.; pulse, 100; respirations, 40 per minute; and blood pressure, 130/100 mm. Hg. The patient was well developed and well nourished and

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Received for publication March 17, 1950.

was orthopneic and extremely anxious. There was moderate cyanosis of the lips and fingernail beds. Respirations were rapid and shallow. The pupils reacted to light and in accommodation. The fundi revealed moderate arteriosclerotic changes. Examination of the chest showed some increase in the anteroposterior diameter, and there were coarse, crepitant râles heard throughout both lungs. The breath sounds at the left base were diminished in intensity. Examination of the heart showed no evidence of enlargement. There was no increase in precordial activity. A loud, harsh, musical systolic murmur was heard loudest in the mitral area and was transmitted into the left axilla and posteriorly to the region of the left scapula. The murmur filled the entire period of systole and ended with the second heart sound. The liver was not palpable but was percussed 7.5 cm. below the right costal margin. There was two plus ankle edema.

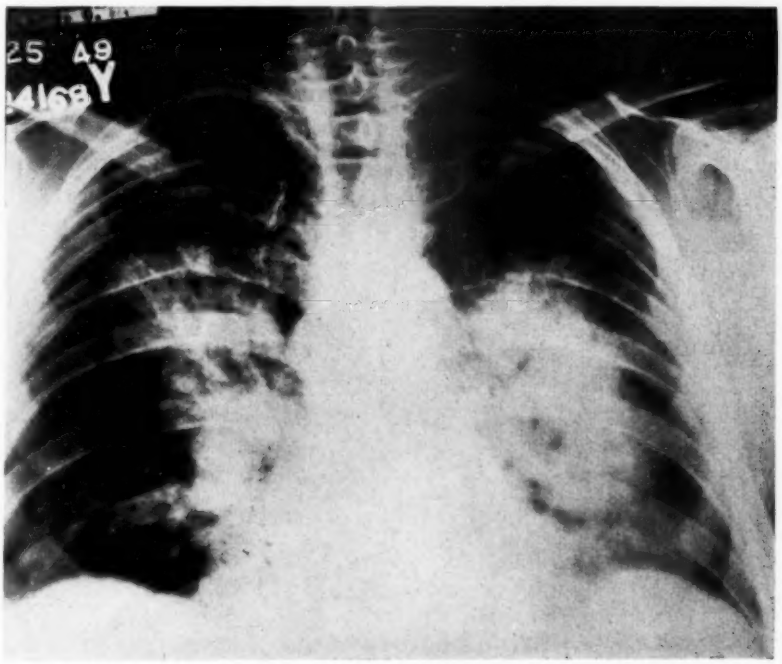

Fig. 1.—Posteroanterior film of chest showing "sunburst" infiltration extending from hila.

Laboratory Findings: Examination of the blood showed a white count of 12,000 with the differential showing a slight shift to the left. There were no abnormal forms. Red blood count was 4.51 million with 14 Gm. hemoglobin. Serology for syphilis, nonprotein nitrogen, blood urea nitrogen, total protein and albumin-globulin ratio, cold agglutinins, examination of the sputum for acid-fast bacilli, and three blood cultures were all negative or normal. Urinalysis was normal on admission, but toward the end of his hospitalization it showed two plus albumin with a few hyaline casts; maximum specific gravity, 1.030. Sedimentation rate was elevated to 38 mm. and remained elevated. Radiographic examination of the chest revealed a bilateral "sunburst" type of infiltration into the central portions of both lung fields extending from the hila (Fig. 1). This infiltration persisted throughout his hospital stay (Fig. 2). Serial electrocardiograms revealed low voltage, a Q_2, Q_3, and Q in aV_F with depression of the ST junction in V_4, V_5, and V_6. Although the Q waves were small, the relative amplitude compared to the total amplitude of the small R wave made the diagnosis of a posterior myocardial infarction highly probable (Fig. 3).

Hospital Course: Because of the evidence of a recent myocardial infarction, the loud systolic mitral murmur, and the persistent severe pulmonary edema and hemoptysis, a diagnosis of ruptured papillary muscle was made. The patient became progressively worse, his symptoms of

cardiac failure responding only slightly to digitalis and mercurial diuretics. He was also treated with antibiotics and anticoagulants. On Nov. 22, 1949, approximately one month after admission, he complained of severe chest pain radiating into the left shoulder. He became markedly dyspneic and in spite of vigorous therapy with positive pressure oxygen and morphine, he lapsed into coma and died.

The final diagnosis was arteriosclerotic heart disease (coronary sclerosis): (a) posterior myocardial infarction with rupture of papillary muscle and secondary severe mitral insufficiency, (b) sinus tachycardia, and (c) Class IV.

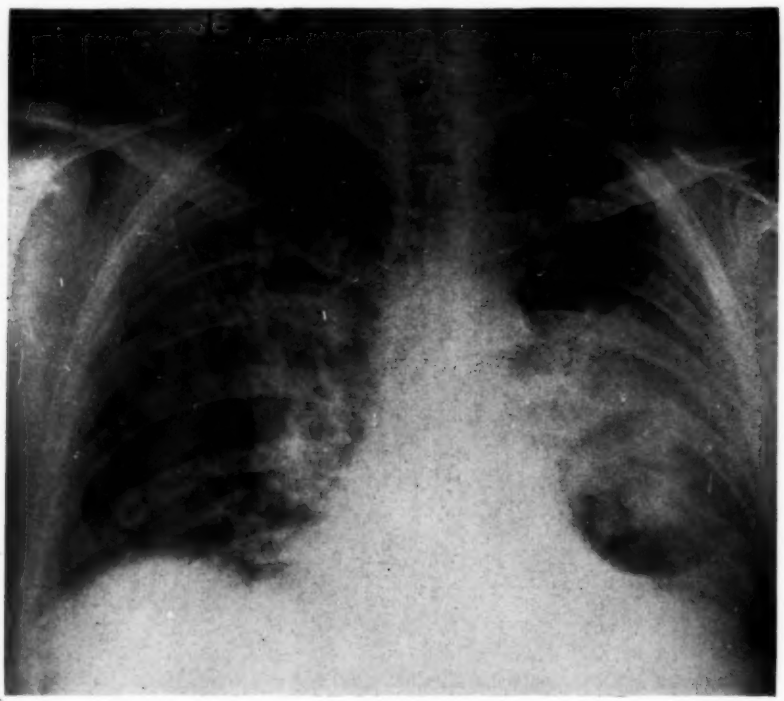

Fig. 2.—Chest film made on twelfth hospital day showing persistence of hilar infiltration.

Autopsy.—

Cardiovascular system: The heart weighed 550 grams. It measured 11 cm. from the atrioventricular sulcus to the apex and 10 cm. in its transverse diameter. The organ was flabby. The epicardium overlying the posterior surface of the left ventricle was thickened, opaque, and covered by a thin layer of fibrin. The myocardium of the right ventricle showed no significant pathologic changes. The myocardium of the left ventricle showed no gross pathologic changes except in the posterior wall where there was an infarct extending from the apex to the base. The posterior papillary muscle was involved in this infarct, and it was ruptured at its base (Fig. 4). There were numerous small mural thrombi in the left ventricle.

There was marked coronary arteriosclerosis, and the lumen of the left circumflex artery was occluded by an organized thrombus. The lumen was occluded by a recent thrombus, 3 cm. from the origin of the right coronary artery.

Respiratory system: Both lungs revealed edema and marked passive hyperemia.

Microscopic Examination.—

Cardiovascular system: On microscopic examination there was both a remote and recent infarct in the posterior wall of the left ventricle. A section through the ruptured papillary muscle

revealed recent necrosis and degeneration of the muscle with beginning endothelial proliferation over its free margins (Fig. 5).

Respiratory system: There was acute and chronic passive hyperemia of all lobes of both lungs with edema and multiple intra-alveolar hemorrhages, some of which were undergoing organization.

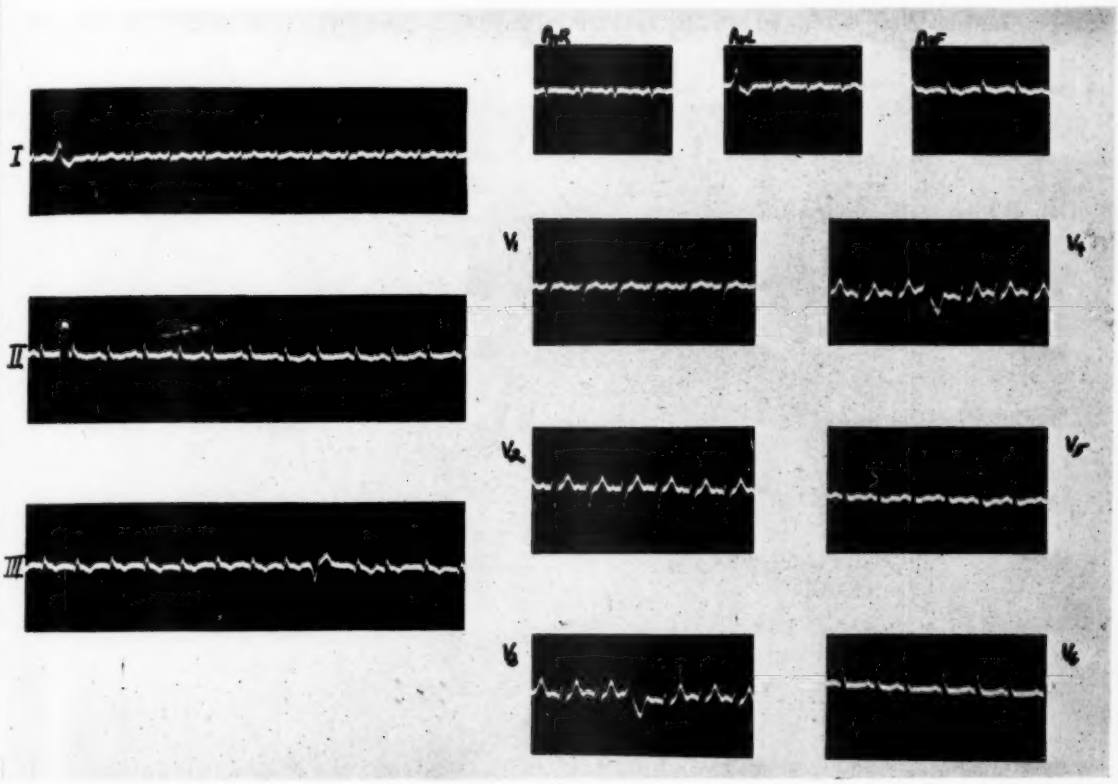

Fig. 3.—Electrocardiogram showing Q_2, Q_3, Q_{AVF}, with inversion of T_2, T_3, and T_{AVF}, suggesting a posterior myocardial infarction.

Pathologic Diagnoses.—

Cardiovascular system: (1) Cardiac hypertrophy and dilatation. (The heart weighed 550 grams.) (2) Old and recent infarcts of the myocardium of the posterior wall of the left ventricle with rupture of the posterior papillary muscle of the mitral valve.

Respiratory system: (1) Acute and chronic passive congestion of all lobes of both lungs, marked, with multiple organizing intra-alveolar hemorrhages. (2) Atelectasis of all lobes of both lungs, marked.

DISCUSSION

The rupture of a papillary muscle in the heart is an uncommon occurrence. Stevenson and Turner,[3] in 1935, state that only two cases were found in 6,000 autopsies at the Baltimore City Hospital, and none were found in 14,000 consecutive autopsies performed at Johns Hopkins Hospital or in the last 2,000 at the University of Maryland Hospital. These authors state that the earliest reported case is that of Merat in 1803 and that Corvisart described another in 1811. Dur-

ing the next century, four more cases were reported in the French literature. In 1887, Osler described a case in which the coronary arteries were "much calcified." Dennig, in 1909, first stressed the fact that coronary disease is probably the principal etiology of these ruptures.[3] However, Davison[2] states that Le Piez, in 1873, had already stressed this relationship. By 1948, twenty-eight cases had been reported, to which Davison added three cases which with ours makes thirty-two cases in all.

Fig. 4.—Heart, looking into left ventricle, showing ruptured papillary muscle.

Etiology.—The most common cause for the rupture of a papillary muscle is coronary artery disease and especially a recent myocardial infarction. If one excludes traumatic rupture,[4,5] the number of instances where it has occurred in the absence of infarction is very small. Bertin, in 1824, reported a case of rupture of the papillary muscle of the right ventricle presumably due to tuberculous vegetations.[3] In 1865, Spanton described one secondary to bacterial vegetations in a case of puerperal sepsis in the right ventricle. Finally, Spalding and Von Glahn at the Baltimore City Hospital described one caused by syphilis, demonstrating *Treponema pallidum* in the myocardium.[3] All the other reported cases were secondary to myocardial infarcts except two where there was severe coronary disease with patchy infarction of the papillary muscle itself,[3,6] and one case secondary to polyarteritis nodosa.[3]

Pathogenesis.—It is logical to assume that any disease which will cause weakening, necrosis, or ulceration of the heart muscle, and consequently of a papillary muscle, could conceivably predispose to its spontaneous rupture. This fact is of utmost importance in making the clinical diagnosis possible. In other words, the predisposing disease must be present and must be recognized. Since myocardial infarction is most commonly the result of coronary disease, it is not difficult to understand why it is by far the most common cause. Bac-

terial vegetations are rare on the muscle itself. Syphilis of the myocardium is extremely uncommon. In those cases where no occlusion had occurred, the cause undoubtedly was coronary insufficiency since these hearts showed marked coronary sclerosis, and there were diffusely mottled hemorrhagic areas in the subendocardial region of the left ventricle. In some instances these patches were

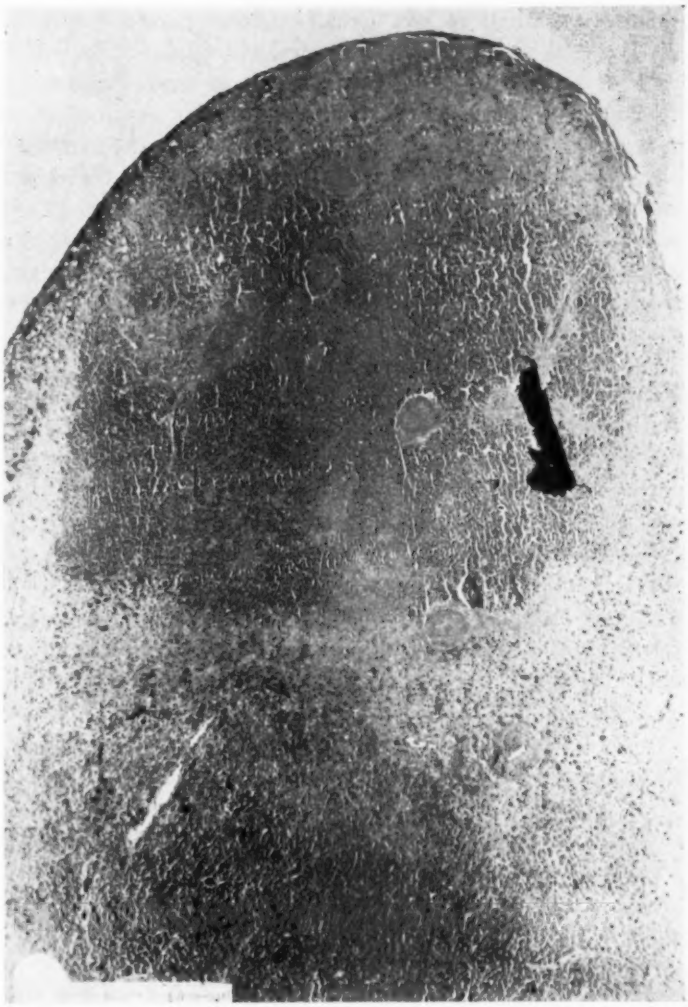

Fig 5.—Photomicrograph showing ruptured margin of papillary muscle with endothelialization.

more confluent, producing patches of myomalacia. Interestingly, the greatest localization was in the region of the posterior papillary muscle of the left ventricle, which explains the predominant localization of these ruptures in this muscle. Of the thirty-two cases described thirty were in the left ventricle, and of the twenty-six in which the exact location was indicated, seventeen were in the posterior, one in both posterior and anterior, and only eight in the anterior

papillary muscle. This has been attributed to the especial remoteness of this region of the heart from its source of blood supply.[2]

Pathologic Physiology.—The relationship between myocardial infarction and the rupture of a papillary muscle has been discussed. It is obvious that it results in a marked mitral insufficiency. In addition, as we shall later emphasize, a marked degree of pulmonary edema develops. It is clinical experience that mitral insufficiency alone does not usually produce it. Why, then, does it appear here? We believe that we have a logical explanation, on the basis of both experimental and clinical grounds. Wiggers and Feil[7] after producing mitral insufficiency experimentally found that: (1) "As long as the cardiac muscle is efficient, the increased volume of blood contained in the left auricle during systolic ejection is accommodated by an expansion of the left auricle and its venous tributaries. Consequently no 'back pressure' effects are produced in the pulmonary artery or the right heart;" and (2) "When arterial resistance is increased in the systemic circuit, the regurgitation volume increases markedly at once, thereby elevating not only the left auricular pressure, but causing also a damming back of blood into the pulmonary artery and right heart— —." Thus as long as the left ventricle is functionally competent, no pulmonary edema should be produced. This was strikingly demonstrated in a case of traumatic rupture of both anterior and posterior papillary muscles of the mitral valve. The coronaries and myocardium both were normal, and there was no evidence of pulmonary edema.[5] In the cases of spontaneous rupture, however, there has been a recent myocardial infarct, the left ventricle is incompetent, severe mitral insufficiency has been superimposed, and severe pulmonary congestion can be expected.

Clinical Picture.—The clinical picture produced by a ruptured papillary muscle in the heart is primarily that of the underlying disease, usually a myocardial infarct. In a good proportion death occurs suddenly, and the diagnosis is impossible. Thus of the nineteen patients described by 1935, nine died suddenly.[3] In those who survived the acute episode however, two specific and striking manifestations appear. A murmur usually appears, which is characteristically loud, harsh, and musical and is heard over the mitral area. In twenty-three of the thirty-two cases (including our own) murmurs were described, of which seventeen were systolic, four both systolic and diastolic, one diastolic, and one systolic at the base. In one case murmurs were present but not described; in one "loud noises" were present; in one[1] a loud "friction" was heard, which could have been a murmur. It must be realized that some of the early cases were described before the present development of auscultation, and so a murmur could have conceivably been present and not been described. The other manifestation which appears and which is strikingly frequent is intractable pulmonary edema. In reviewing the clinical pictures of the previously described cases it became obvious that this was a very frequent occurrence. In many of the patients hemoptysis and frothy bloody sputum were the initiating symptoms. Lowry and Burns[1] emphasized that their patient had marked pulmonary edema and cyanosis. Davison's patients had pulmonary edema[2]; Lipscomb's patient had "marked pulmonary congestion." Moragues[8] describes a patient

in whom the "lungs showed an extreme degree of edema . . . On cut section, a large amount of serous frothy fluid oozed from the parenchyma." In our patient the pulmonary edema was the most striking clinical feature, and it was intractable, showing very little response to treatment. We believe, then, that the most frequent clinical picture of a ruptured papillary muscle in the left ventricle is that of the underlying predisposing disease, namely a myocardial infarction, plus the development of a loud mitral murmur, plus the signs and symptoms of intractable pulmonary edema. It need only then be differentiated from ruptured chordae tendineae, a ruptured mitral or aortic valve, perforation of the interventricular septum, and the coexistence of a myocardial infarct in a previously existing rheumatic mitral insufficiency. Rupture of the chordae tendineae can be eliminated as a possibility in the absence of bacterial endocarditis, since the chordae are affected by vegetations while the muscle is affected by infarction. A ruptured mitral or aortic valve can be dismissed on the basis of the predisposing disease and the location of the murmur. A rupture of the interventricular septum in the course of a myocardial infarction may closely simulate a ruptured papillary muscle, but the murmur is best heard in the third and fourth left interspaces parasternally and is not transmitted into the axilla, and pulmonary edema is not as striking. Furthermore, electrocardiographic evidence might show conduction disturbances in the septal lesion and help in the differentiation. The coexistence of a myocardial infarction and a pure rheumatic mitral insufficiency without stenosis could conceivably present a similar picture. Pulmonary edema is less likely, however, and the murmur less widely transmitted. Furthermore, the murmur develops after a latent interval following the infarction. Enough time must elapse to allow necrosis of the muscle before rupture occurs. It is interesting, therefore, that our patient had had epigastric pain which he described as "gas pain" five days prior to the onset of his marked dyspnea and pulmonary edema. The history is therefore helpful and often conclusive.

SUMMARY

1. A case of rupture of a papillary muscle in the left ventricle is presented.

2. The etiological relationship of myocardial infarction is stressed.

3. The striking frequency of pulmonary edema and the mechanism of its cause are discussed.

4. It is suggested that the appearance of a loud mitral systolic murmur and marked intractable pulmonary edema in the course of a myocardial infarction produces a syndrome which should make the clinical diagnosis of a rupture of a papillary muscle in the left ventricle tenable.

ADDENDUM

Two additional cases of ruptured papillary muscle of the left ventricle were recently reported by Smith.[9] These were also associated with myocardial infarction.

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AIR TRAVEL AND THE CARDIAC PATIENT

An Analysis of Relevant Experimental and Empirical Data

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New York, N. Y.

THE majority of patients who confront their physicians with the question of the advisability of their flying are those whose hearts have been damaged by age or by disease. It is assumed that at the time of inquiry the patient's heart condition is reasonably compensated, and that the question applies to the would-be passenger on an average commercial plane. The problem then is the one of the specific hazards of flying for patients suffering from heart ailments.

There is little that has been proved pertinent to the inherent problem. Textbooks deal with it only sparingly. Prevailing opinion is based mostly on theory and conjecture. Conclusions have been drawn from experiments which either have no similarity to actual flying conditions or which leave much leeway for interpretation.

In 1938, while studying electrocardiographic evidence, a group of workers at Columbia University, New York,[1] issued this warning: "Persons known to have cardiac disease due to an affection of the coronary arteries should not be permitted to ascend to high altitudes." They continued that, in instances where flight is imperative, oxygen should be supplied. In 1940, another warning was delivered by White,[2] based on the fact of electrocardiographic changes induced in actual flight. Graybiel,[3] in 1941, stated that there is much evidence that a person with a normal, or even a diseased, heart may withstand surprisingly severe degrees of oxygen lack without injury. Friedberg[4] observed that most patients with angina pectoris tolerate usual commercial flights.

Therefore, it is appropriate to re-evaluate available data and to attempt a clarification of the question of whether or not it is justified to permit air travel for patients with heart ailments.

Individual resistance to altitude may be regarded as the chief problem in flying. Other factors, like speed and rapidity of ascent or descent, involve no appreciable risk to the circulation in commercial air traffic. Possibly fear and apprehension are quantities to be reckoned with. However, anyone who has flown knows how quickly this feeling is replaced by exhilaration and pride in the conquest of the air.

Altitude tolerance in healthy individuals has been studied extensively. Experiments in low-pressure chambers, reproducing conditions of varying altitudes, register reactions of body and mind to be expected in altitude flight. Physical and mental integrity begin to show impairment at levels as low as 7,000 feet in some cases, but impairment is generally evident at levels nearer to 15,000

Received for publication June 16, 1950.

feet, which approximates a 12 per cent oxygen tension of the inhaled air. Sensations of lightheadedness appear, breathing is deepened, pulse rates are increased, and mental alertness is decreased. Blood pressure reactions vary individually; more frequently the blood pressure is moderately raised, less often it is unaltered, and in some cases it is slightly lowered. It should be mentioned that cross-country and overseas travel proceed quite regularly at levels of 10,000 feet. A number of experiments reveal individual resistance to much higher altitudes without the benefit of additional oxygen. Known deaths from anoxia occurred at an average height of 27,000 feet, probably depending also on the duration or exposure to these levels.[5]

Experiments of German investigators[6] brought to light the important fact that altitude tolerance uniformly increases with advancing age. This should not be surprising. Variations in the oxygen tension and in acid-base equilibrium of the blood are chiefly controlled by the autonomic nervous system, specifically the chemoreceptor fibers located in the aortic and carotid bodies; blood pressure deviations are controlled by pressure receptor fibers of the aortic nerve and the carotid sinus. It must be thought that the challenge to these nerve structures, which is ever increasing with age, leads to a higher degree of effectiveness. The reflexes become even more alert when pathological conditions, such as circulatory or respiratory distress, demand their constant vigilance.

The statement by Levy and associates quoted previously,[1] that persons with coronary disease should not be permitted to ascend to high altitudes, was prompted originally by two incidents, one of pulmonary edema and one of circulatory shock, which occurred in the following experiment of thirty-seven test cases. Patients known to suffer from coronary artery disease were placed abruptly in a chamber containing 12 per cent oxygen for a period of twenty minutes. This procedure does not reproduce flying conditions. It more nearly represents a jump from sea level to an altitude of 15,000 feet. It does not allow the adaptor organs of the body to function as they would in gradual ascent. Theoretically at least, the risk involved in such a procedure seems apparent. However, the same workers, and many others subsequently, have been able to continue the same type of experimentation even with lower oxygen levels up to the present with only a few unfortunate happenings reported. Actually, though unintentionally, a strong argument for the high altitude tolerance of cardiac patients is furnished by this possibility of performing routine experiments with the anoxemia test.[7] Ten per cent oxygen in the inhaled air is now recommended for this test, designed to detect significant features in the electrocardiogram for the purpose of differential diagnosis. This oxygen level corresponds to an altitude of 17,000 feet; the alveolar oxygen pressure at this level is cut in half. The procedure may be pictured thus: A patient known to suffer from coronary artery disease is, within the period of a few minutes, magically lifted to an altitude well above that of the highest summit in Europe, to stay there for twenty minutes. (Mt. Whitney, the highest mountain in the United States, is 15,000 feet high, and Mont Blanc in France is 15,800 feet.) Is there any other experiment which would offer more convincing proof of the extraordinary altitude tolerance of patients with cardiac disease?

White[2] recorded electrocardiograms in healthy flyers during actual flights at different altitudes. The changes so produced were taken to be indicative of myocardial involvement, and support was given, therefore, to the theory that myocardial anoxemia is a contributing factor in the production of coronary artery symptoms. Previous to this statement, however, it was shown by the author[8] that electrocardiographic changes, known to occur by gradually inducing oxygen want in a rebreathing chamber, are even greater in younger and athletic individuals than in the older age groups. The degree of T-wave flattening was found to be 75.3 per cent in subjects 15 to 20 years of age, 63.7 per cent, 49 per cent, and 20.2 per cent, respectively, in each following decade, and 16.1 per cent between the ages of 50 and 70. It was then suggested that the greater changes occurring in the strong and healthy are associated with greater adaptability. Conversely, the lack or absence of changes in older and enfeebled persons was said to indicate either an inability to compensate for lower oxygen tension or a failure to react electrocardiographically to the stimulus of oxygen lack because of their frequent exposure to anoxemia. It seems now that the latter mechanism has the greater probability, the greater changes in the young demonstrating the greater need and/or ability for adaptation. Unquestionably, marked changes in the electrocardiogram frequently occur after induced anoxemia in patients suffering from heart disease. These changes, however, are of a somewhat different type than the concordant T-wave and S-T changes in the normal heart; also, the return to the original tracing after release from oxygen want is usually slower than in the healthy subject. The changes observed in heart disease are discordant, bizarre, and sometimes paradoxical (elevations of previously inverted T waves). The discordant deviation in the anoxygram from patients with cardiac disease is most likely due to the disturbance of the electrical gradient by myocardial fibrosis, superimposed upon the concordant changes produced by the anoxemia. A. E. Cohn[9] compared these changes with the lopsidedness of an old-fashioned scale out of balance. Whether a concordant or a discordant type of electrocardiogram is obtained, the electrocardiographic response to anoxemia can be excluded as evidence of traumatization of the heart, caused by temporary oxygen lack. Objections to altitude flying based upon changes in the electrocardiogram can be discarded.

Although it seems logical to assume that patients suffering from heart conditions should react poorly to oxygen want, proof of this is not forthcoming by reports of accidents of the cardiovascular system in commercial air traffic. An extensive inquiry was undertaken by Graybiel,[3] in 1941, at a time when oxygen equipment on commercial planes was still largely lacking and pressurized chambers were not yet in use. Data were collected from five major airlines on seven million passenger flights. Only three deaths had occurred aloft; the cause in each case was ascribed to heart failure. The first passenger had died from sudden heart failure at an altitude of 3,000 feet; the relationship between flight and death was considered accidental. The second passenger, 80 years of age, had died while flying at an altitude of 12,000 feet. The third passenger had boarded the plane from an ambulance upon the written release of her physician. Out of five cases who died after leaving the plane, two were ascribed to heart failure.

The experiences gained through the evacuation of the sick and wounded from combat zones in World War II should help to evaluate the risks involved in altitude flying for any physical ailment. From January, 1943 to November, 1945, the Air Transportation Corps of the armed services evacuated more than 220,000 patients.[10] Such flights often proceeded under trying conditions and necessitated long overseas travel. To summarize this experience, two quotations may be cited: "There are few absolute contraindications to transportation of patients by airplane,"[11] and "The air evacuation program of the military services has demonstrated that patients who may be transported at all may safely travel by air."[12]

A fatal cardiac attack of a 35-year-old pilot was reported by Benson in 1937.[13] The altitude at which the episode occurred was not given. Autopsy revealed advanced coronary arteriosclerosis and multiple abnormalities. The paucity of similar reports is striking. Of clinical rather than aeronautical interest is a report which describes an extraordinary altitude tolerance (over 20,000 feet without additional oxygen, in combat) of a pilot who was suffering from an asymptomatic congenital complete heart block.[14]

Any motorized locomotion may aggravate a cardiac condition by producing motion sickness. It would be of value to have statistics available on circulatory accidents in trains or boats. Recently the captain of a medium-sized ocean liner reported three deaths on one particularly stormy Atlantic crossing; all three deaths were attributed to heart disease.[15]

COMMENT

The accumulation of physiological, experimental, and empirical data now available strongly suggests the presence of a factor in the human body which increases tolerance to oxygen want in the aged and in those with cardiac disease. It seems likely that the alerted adjustor mechanism of the carotid and aortic nerve structures plays a greater role in the emergency of oxygen want. Some of the mechanisms which participate in the adjustment of the body to high altitude, besides the well-known acclimatization by polycythemia to altitude sojourns, are, according to Wiggers,[16] increased cardiac output and vital capacity, a slight shift of the pH of the blood, and an increased capacity of the blood to fix and use oxygen. There is also evidence that the coronary vessels dilate. "Continuing dilatation of the coronary vessels seems to be a provident mechanism which compensates for diminishing volumes of oxygen carried by each c.c. of blood."[16] Probably all of these processes are mediated through the activities of the nervous apparatus described above. As could be expected, there is evidence also that the hypophysis and adrenal glands are called into play.[17]

However, the apparently increased tolerance to oxygen lack in the aged and in patients with long-standing cardiac conditions might be lowered by associated conditions present in the same individual, for instance, by reduced vital capacity from pulmonary lesions or by decrease of oxygen carrying-power of the blood from blood dyscrasias. It should be remembered in this connection that thyroid disease is characterized by an increased susceptibility to oxygen deficiency. Yet all these considerations lose their validity when air travel is contemplated

where oxygen is readily available or where the cabin is pressurized. That motion sickness may aggravate a circulatory malfunction is equally true for any kind of motorized transportation. Considering the fact that three times as much oxygen is needed when walking at the rate of two miles per hour than when at rest, it is easily understood that cardiacs in air travel should refrain from undue exertion. It is self-evident also that the regulations of diet should be identical with those when not flying; it should be kept in mind that not eating enough because of ensuing hypoglycemia may be just as harmful as overindulgence in food.

Many experiences show that altitude flights by cardiac patients are tolerated unexpectedly well. Because of their significance, three case reports follow.

CASE REPORTS

CASE 1.—A 77-year-old man, J. W., who had suffered at least four major attacks of coronary thrombosis during the past twelve years, was eager to go on his yearly fishing trip to Canada. He disregarded medical advice, insisting upon the trip; his only compromise was his request that his physician accompany him. He suffered from severe coronary insufficiency; walking up a slight incline provoked anginal pain. His heart and aorta were grossly enlarged. His electrocardiogram showed marked myocardial damage. His blood pressure varied from 160 to 120 mm. Hg systolic and 60 to 50 mm. Hg diastolic. Albuminuria was 2 plus. When at rest, he evidenced no cardiac decompensation. During the flight from Montreal to Quebec, the pilot of the small plane ascended to 11,000 feet rather suddenly in order to evade a menacing storm center. The patient was watched closely. His pulse, respiration, and general well-being were not impaired in the slightest. Other passengers in the plane, as well as the physician himself, were distressed. At the fishing camp, the guide and the physician had to carry the man from the boat dock to the cabin regularly because of the small incline about fifty yards long which caused him pain. It may be added that the patient made yearly trips to Florida by plane without ill effects.

CASE 2.—F. R. H., aged 73 years, a retired admiral of the United States Navy, experienced a coronary thrombosis six years ago. His heart was enlarged, his blood pressure normal or subnormal. His electrocardiogram showed myocardial damage and moderate atrioventricular block. Albuminuria was 1 plus. He was moderately overweight. He experienced anginal pain on occasion, once or twice a week. He was very active as a consulting engineer. Approximately two years ago, after a flight to Mexico, he related the following story: The Mexican government had placed a small military plane at his disposal; the ambitious young pilot was eager to give the admiral a birdseye view of Mexico City, which is itself 7,500 feet above sea level. Much to the annoyance of the admiral, the plane ascended to an altitude over 12,000 feet. However, to his own surprise, he tolerated the altitude extremely well. One year ago, this same patient made a quick air trip to Guam without the slighest impairment of his general condition.

CASE 3.—E. H., aged 72 years, also a consulting engineer, exhibits an advanced general arteriosclerosis and calcific aortic valve disease. He is a short, stocky, overweight man with a blood pressure of 165/40 mm. Hg. His heart is enlarged; his cardiac sounds are muffled and distant; and a harsh systolic murmur is heard at the base. His palpable pulses are rigid. His electrocardiogram shows deep ST depressions in Leads I and IV; T_1 and T_4 are deeply inverted and cove-shaped. He has marked pulmonary emphysema with dyspnea. His hemoglobin is 100 per cent; the erythrocyte count is 5,500,000. Albuminuria is 2 plus. He has slight pretibial edema. During the past three years alone this patient has accomplished 56,000 miles of air travel, including two trips to Brazil and one to Turkey. Most of these flights were in pressurized cabins. Only once, on a rough hop from San Francisco to Denver in a two-motored, nonpressurized plane, flying well over 11,000 feet, he experienced headaches but never chest pains. His headache was immediately relieved by oxygen. He is about to fly to Turkey again in the near future.

CONCLUSION

A reappraisal of pertinent data and many experiences, including those of the air evacuation program of the armed services during the recent war, requires

a new and modified attitude on the part of the physician. At the usual altitudes of commercial air traffic, the risk involved in flying for patients with heart ailments is definitely less than is generally supposed. With the added safety of pressurized cabins, even flight well above the common level represents no special hazard to the cardiac patient. Whenever a patient is ready for travel, flying is a thoroughly feasible means of transportation.

SUMMARY

The fundamental principles in flying have been reviewed. Special reference was given to the evidence that people of advanced age and those with heart disease exhibit an apparently increased tolerance to oxygen want. It was explained why electrocardiographic changes, induced by anoxemia, do not reflect cardiac traumatization. However, the possibility of testing patients with cardiac disease under very low oxygen pressures as a routine procedure was held to be a strong argument for the high altitude tolerance of these patients. The collective experience of the airlines, as well as the crucial experiment of the air evacuation of the sick and wounded from combat zones during the recent war, was found to corroborate this view. Three interesting case histories were given. It was concluded that (1) a strong augmented adjustor mechanism probably protects the cardiac patient from the harmful effects of low-oxygen tension in the inhaled air; and (2) there is no valid objection to travel in modern air vehicles for the patient suffering from heart disease.

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THE EFFECT OF L-NOR-EPINEPHRINE UPON THE CORPUSCULAR VOLUME AND HEMATOCRIT

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NOR-EPINEPHRINE is chemically different from epinephrine only in lacking a methyl group on the nitrogen atom. Extensive investigations have been made of its actions in relation to adrenaline[1] and especially sympathin E.[2-5] No study, however, of the effect of l-nor-epinephrine upon the corpuscular volume and large vein hematocrit has been undertaken. In the case of adrenaline, use of radioactive tagged erythrocytes has shown that the rise in hematocrit following adrenaline administration is not attended by a detectable increase in corpuscular volume.[6,7] A redistribution of a portion of the cellular constituents from the adrenaline-contracted smaller vessels to the larger vessels has been held responsible for the elevated hematocrit. Since nor-epinephrine is a powerful, but probably not pure, peripheral vasoconstrictor and as such may have a role as a therapeutic substance, a study of its effects upon the corpuscular volume was indicated.

The following investigation was thus undertaken to determine what effect the intravenous administration of l-nor-epinephrine to adult human beings has upon the large vein hematocrit and the corpuscular volume as measured by the P_{32} technique. We are indebted to Professor Euler of the Karolinska Institutet, Stockholm, for the l-nor-epinephrine and to the Swedish Medical Board for the radioactive phosphorus.

METHOD

Ten subjects were examined, eight men and two women. All were young and possessed normal cardiovascular systems; one individual had a low-grade diabetes mellitus. Following a brief explanation of the procedure, the subjects rested in a chair-bed for one-half hour. An indwelling needle was introduced into an antecubital vein, and a small amount of heparin solution injected into the needle so that clotting did not occur. Another period of rest ensued, and then some of the patient's own blood previously activated to a measured degree with radioactive phosphorus by the method of Hahn and Hevesy[8] and Nylin[9] was injected. Ten minutes later a sample of blood was drawn for the determination of the resting blood activity and hematocrit. L-nor-epinephrine, 0.07 mg.

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Received for publication Jan. 26, 1950.
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in 10 c.c. of saline, was then slowly injected intravenously over a five-minute period and the pulse and blood pressure recorded at minute intervals before, during, and after the injection. Repeated samples of blood were taken immediately after the injection and at intervals during the following hour.

The hematocrit was determined in duplicate or triplicate, centrifuging at 3,000 r.p.m. for thirty minutes. Two portions of each blood sample were centrifuged, and the red cells washed with plasma, dried, pulverized, weighed into counting capsules, and the activity per unit of weight of dry corpuscles measured by a standard Geiger-Müller apparatus.

RESULTS

In all cases the administration of the l-nor-epinephrine caused a definite elevation of both systolic and diastolic pressures with bradycardia for the duration of the injection. For the group the mean heart rate was decreased by eighteen beats per minute while the mean systolic and diastolic pressures were elevated 23 and 17 mm. Hg, respectively. The mean results of the serial determinations of the large vein hematocrit and radioactivity per unit of dry weight of erythrocytes are presented in Table I. The standard deviation of the repeated hematocrit values obtained at rest, after reduction to a percentage of each individual's mean, was 0.77 per cent. On this basis the 2.3 per cent elevation occurring one to two minutes after the injection of the nor-epinephrine is, although small, a significant ($P = 0.02$) elevation of the hematocrit; the 2.0 per cent elevation is probably significant ($P = 0.035$). The remaining two altera-

TABLE I. EFFECT OF NOR-EPINEPHRINE ADMINISTRATION UPON THE VENOUS HEMATOCRIT AND THE ACTIVITY PER GRAM OF DRY ERYTHROCYTES EXPRESSED AS PER CENT OF RESTING LEVEL (MEAN VALUES FOR GROUP)

	RESTING LEVEL	MINUTES AFTER L-NOR-EPINEPHRINE			
		1 TO 2	8 TO 15	20 TO 30	31 TO 50
Hematocrit value	100 (S.D. = 0.77)	102.3	102.0	98.3	98.3
"t"		3.0	2.6	1.7	1.7
P		0.02	0.035	0.12	0.12
Impulses per gram of dry red blood cells					
Observed	100	96.6	97.7	95.7	94.9
Anticipated	100 ± 2.25%	98.1	97.2	96.3	95.2

The values of "t" and P refer in each case to the respective hematocrit value in comparison to the resting value of 100 and where n = 7. S.D. = $\sqrt{\frac{\Sigma x^2}{(n-1)}}$; $\pm t = \frac{(\bar{x} - m)}{S_{\bar{x}}}$. The probability, P, was obtained from standard tables for the distribution of "t." (Fisher, R. A., and Yates, F.: Statistical Tables for Biological and Medical Research, Oliver & Boyd, Ltd., London.)

The anticipated values of activity per gram of red blood cells represents the decrease of activity for each time period considered calculated on the basis of 3.5 per cent straight line decline for the first hour after injection of P_{32} tagged erythrocytes. Error of method = ± 2.25 per cent (4.5 per cent total).[10]

tions are not significant. In respect to each of the seven individuals the noradrenaline infusion caused significant elevation in five, moderate elevation in one, and no change in one.

The mean of the observed values for activity at each respective time interval is expressed as a per cent of the control resting level. Since erythrocytes tagged with P_{32} by the method employed normally lose at a constant rate approximately 3.5 per cent of the isotopic phosphorus during the first hour after injection, the relative activity anticipated at the respective intervals after injection is presented (thirty minutes between tagged erythrocytes injection and the one to two minute sample). The mean activity of the observed samples, as presented in Table I as well as in each individual case, fell within the limits set by the experimental error of this procedure, ± 2.25 per cent[10] of the anticipated value.

TABLE II. EFFECT OF NOR-EPINEPHRINE ADMINISTRATION UPON THE VENOUS HEMATOCRIT AND CIRCULATING RED CELL MASS

SUBJECT		RESTING LEVEL	MINUTES AFTER L-NOR-EPINEPHRINE			
			1 TO 2	8 TO 15	20 TO 30	31 TO 50
1 A. R.	H	42.2	43.5	44.3	42.0	41.7
	I	1700	1580	1615	1555	1550
2 G. S.	H	46.2	47.2	46.0	45.0	44.0
	I	1030	1001	1055	1035	1020
3 F. M.	H	40.2	42.5	41.5	42.0	42.0
	I	1495	1458	1400	1409	1396
4 D. F.	H	43.0	43.5	42.0	41.0	41.5
	I	2170	1977	1978	1950	1905
5 J. K.	H	——	——	——	——	——
	I	1227	1200	1195	1170	1155
6 A H.	H	——	——	——	——	——
	I	305	300	301	302	301
7 B. R.	H	——	——	——	——	——
	I	2506	2492	2512	2408	——
8 I. W.	H	——	——	——	——	——
	I	1135	1156	1139	1139	1173
9 H. B.	H	——	——	——	——	——
	I	677	656	656	645	614
10 O. T.	H	36.5	——	37.0	35.0	35.0
	I	——	——	——	——	——
11 D. F.	H	36.0	——	37.0	35.0	35.0
	I	——	——	——	——	——
12 F. M.	H	43.5	43.3	45.5	43.0	43.5
	I	——	——	——	——	——

H = venous hematocrit.
I = impulses per gram of dry erythrocytes.

An example is presented in Fig. 1 which shows the observations in a 27-year-old physician. The injection of 0.07 mg. of nor-epinephrine intravenously in five minutes raised the blood pressure from 140/85 to 168/105 mm. Hg and slowed the heart rate from 90 to 64 beats per minute. At the end of the injection the peripheral venous hematocrit had risen from 40.0 to 42.5, while the activity per gram of dry erythrocytes showed no significant change from the anticipated levels in serial samples.

DISCUSSION

By employing duplicate samples for measuring the activity of the blood corpuscles, this method of measuring changes in the actively circulating red blood cell mass is accurate to 4.5 per cent.[10] Within such limits the findings of this study indicate that nor-epinephrine, like epinephrine, does not cause red blood cells to be added to or taken from the actively circulating red cell mass. If this had occurred to an extent detectable by this method and if stored cells which would contain no radioactive phosphorus had been added to the circulation, this would have caused a decrease in the activity per gram of red blood cells.

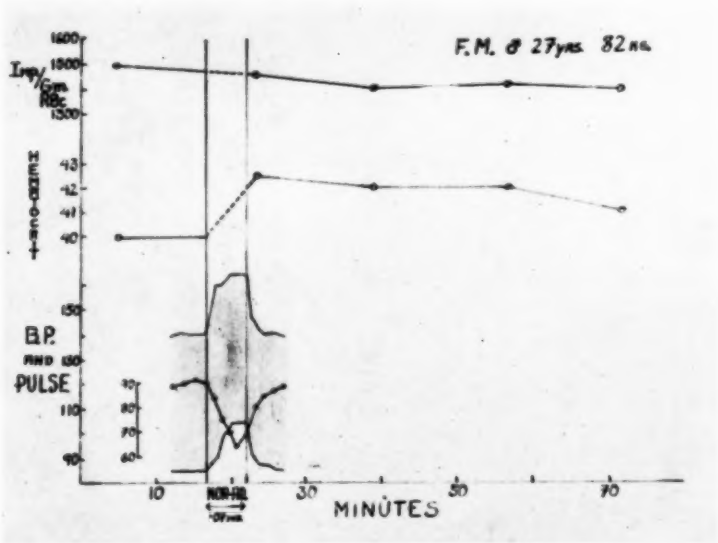

Fig. 1.—The effect of the administration of 0.07 mg. l-nor-epinephrine intravenously upon the blood pressure, heart rate, venous hematocrit, and circulating red cell mass of a normal young man.

A moderate elevation of the large vein hematocrit occurred rather frequently after nor-epinephrine. This change, accompanied by no detectable increase in the actively circulating corpuscular mass, is in keeping with the results which might be anticipated of a peripheral vasoconstrictor from the studies of Hahn[6] and others.[11] Such vasoconstrictor actions result in a redistribution of the blood constituents with the cells being shifted toward the larger vessels and a relative increase in the amount of plasma in the very small vessels throughout the body.

The ability of nor-epinephrine to raise both diastolic and systolic pressures makes its clinical use in cases of shock plausible. It must be noted, however, that these actions of nor-epinephrine produce the same effect upon plasma distribution as does adrenaline. It has previously been pointed out[6] that one of the over-all effects of adrenaline is a withdrawal of a portion of plasma from the actively circulating blood stream, shifting it to the smaller vessels of the periphery and, in part, to the interstitial compartment, and that this may contraindicate the use of adrenaline in certain types of shock. Therefore, on the same basis, it may not be judicious to use nor-epineprine in the therapy of the same types of shock where effective withdrawl of some plasma is not to be desired.

SUMMARY

1. The administration of l-nor-epinephrine to human beings caused a moderate elevation of the large vein hematocrit in five out of seven individuals. This change was not accompanied by any alteration in the circulating corpuscular volume as measured by the tagged erythrocyte technique.

2. The physiological processes which may be responsible for these observations are presented.

Acknowledgment is gratefully made to Professor H. Davis, Department of Mathematics, Northwestern University, for aid in the statistical portion of this paper.

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THE ACTION OF NOR-EPINEPHRINE AND OF EPINEPHRINE ON THE VENTRICULAR RATE OF HEART BLOCK

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IN 1895, Oliver and Schafer reported the potent cardiovascular effects of extracts of adrenal medulla. Their demonstration of this "extraordinary effect upon the tone of the heart and arteries transcending that of any known drug" led to the conclusion that the adrenal glands produced a very active hormone, and these studies may be regarded as initiating endocrine research. The subsequent ten years saw the isolation of the active substance, the elucidation of its chemical structure, and the synthesis of epinephrine. The similarity between the effects of stimulation of the sympathetic nervous system and the action of epinephrine was noted. Since that time, several hundred chemically related compounds possessing a sympathomimetic action have been synthesized. These investigations still continue and have resulted in the introduction of many valuable therapeutic agents. However, epinephrine has remained the only sympathomimetic substance occurring naturally in the body.

Recently a most important development has been the evidence of the presence in the body of nor-epinephrine, an active sympathomimetic compound, closely related in structure to epinephrine. Nor-epinephrine (nor-adrenaline, Arterenol, non-methylated adrenaline) differs from epinephrine only in the absence of the N-methyl group (Fig. 1). von Euler[1] has demonstrated with considerable probability that nor-epinephrine is present in relatively large amounts in mammalian sympathetic nerves and ganglia and is widely distributed in blood and practically all tissues. His work indicates that there are two chemical mediators of the sympathetic nervous system, nor-epinephrine related predominantly to excitor effects and epinephrine related to both excitor and inhibitor functions. This replaces the concept of Cannon and Rosenblueth[2] of two hypothetical cellular substances, sympathin E and sympathin I, formed in the effector cells. The presence of nor-epinephrine in extracts of normal adrenal glands has been clearly shown by Goldenberg and his associates[3]. They also demonstrated that up to 90 per cent of the content of an adrenal medullary tumor may be nor-epinephrine. A further step in the development of nor-epinephrine has been the resolution of the racemic compound and the preparation of the levo-isomer.[4] This is of importance for future investigation since nor-epinephrine, if it is a true sympathetic mediator, should be present in the body in the levo form, as levo-isomers are generally more active. In the case of epinephrine, the naturally occurring substance is the levo-isomer. The separation of levo-nor-epinephrine

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Received for publication April 19, 1950.
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from the natural U. S. P. epinephrine has been accomplished,[5] and a levo-nor-epinephrine content up to 17 to 18 per cent has been demonstrated in U. S. P.-grade natural epinephrine from several sources.[6]

Recently it was demonstrated in man that the hypertension induced by nor-epinephrine was not associated with an increase in cardiac output. However, there was consistently an increase in cardiac output associated with the pressor action of epinephrine.[7] Since the difference in the cardiac actions of nor-epinephrine and epinephrine might have physiologic and pharmacologic implications, it seemed desirable to study the effect of these compounds on another property of the heart, the pacemaking or rhythmic function. The ventricular rate in patients with complete heart block serves as an excellent test organ for this purpose[8] as (a) the ventricular rate in heart block is relatively stable and uninfluenced by extraneous factors, and (b) the sympathomimetic compounds are the only substances which effectively increase the activity of the ventricular pacemaker.

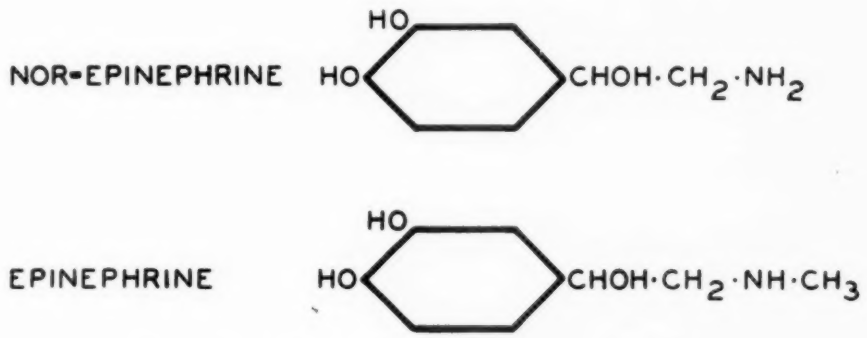

Fig. 1.—Chemical structures of nor-epinephrine and epinephrine.

METHOD OF STUDY

The effect of nor-epinephrine and epinephrine on the ventricular rate of complete heart block was studied in ten patients. Levo-nor-epinephrine hydrochloride was used on all patients and commercial levo-epinephrine hydrochloride (adrenaline) on four patients. In six patients, synthetic levo-epinephrine was administered as the bitartrate. The synthetic compound was substituted following the report of the presence of nor-epinephrine in adrenal extracts used in the commercial preparation. A control electrocardiogram was first made and three blood pressure readings recorded. In three patients 1 c.c. of Ringer's lactate solution was injected intravenously prior to the administration of the compounds to determine the effect of an intravenous injection on the blood pressure and ventricular rate. This procedure produced no significant reaction. The compounds were administered in doses of 0.03 mg. by a rapid intravenous injection. A continuous electrocardiogram was made and blood pressures recorded after 30 seconds and thereafter at one-minute intervals. The observa-

tions were continued for several minutes after the ventricular rate and blood pressure had returned to the pre-injection levels.

RESULTS

There was a striking difference in the reactions following the administration of the two compounds. Within thirty seconds after the intravenous injection of nor-epinephrine, there was an abrupt rise in the blood pressure which lasted from five to eight minutes. The pressor response was greater than that induced by epinephrine in five patients and approximately the same in five patients. The ventricular rate showed only a slight and transient increase. The average increase in the ventricular rate in the ten patients was five beats per minute. Following the administration of epinephrine, there was a marked and sustained increase in the ventricular rate, the average increase being 29.3 beats per minute. Figs. 2 to 6 show typical reactions following the administration of the two compounds. Table I shows the maximum increases in ventricular rate following the administration of the two compounds. The difference in the responses is actually more striking than is shown in this tabulation, as the increase in the ventricular rate following the administration of nor-epinephrine was of relatively short duration as compared with the reaction following epinephrine.

TABLE I. TABLE SHOWING THE MAXIMUM INCREASE IN THE VENTRICULAR RATE IN BEATS PER MINUTE AFTER THE INTRAVENOUS INJECTION OF NOR-EPINEPHRINE AND EPINEPHRINE

CASE	NOR-EPINEPHRINE	EPINEPHRINE
1	5	8
2	−8	18
3	6	28
4	5	44
5	3	22
6	4	20
7	3	26
8	11	38
9	7	29
10	9	40

DISCUSSION

There is a striking difference in the cardiac actions of nor-epinephrine and epinephrine as indicated by the response of the ventricular rate. Nor-epinephrine has a potent pressor action but shows a minimal stimulating effect on the ventricle. It is possible that the transient and slight increase in ventricular rate observed is secondary to the sudden rise in arterial pressure and is not due to a direct action on the ventricular pacemaker. It is known that a sudden rise in intraventricular pressure, such as follows compression of the aorta, increases the activity of ventricular rhythmic foci. In contrast to nor-epinephrine, epinephrine possesses both a potent pressor and cardiac stimulating action. Although our studies deal with the effects on the rhythmic property of the heart, they support the

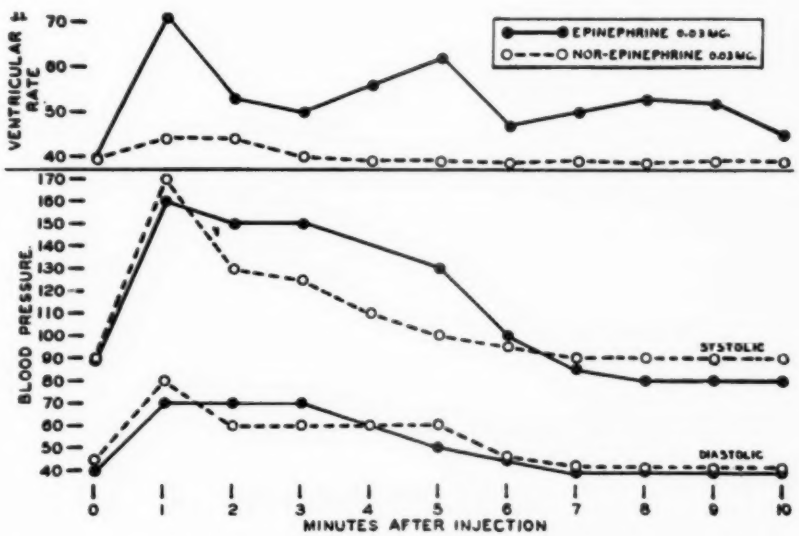

Fig. 2.—Patient J. I. Blood pressure and ventricular rate following the intravenous administration of 0.03 mg. of nor-epinephrine hydrochloride and epinephrine hydrochloride. This illustrates the slight and transient increase in the ventricular rate following nor-epinephrine as compared with a marked and sustained rise following epinephrine.

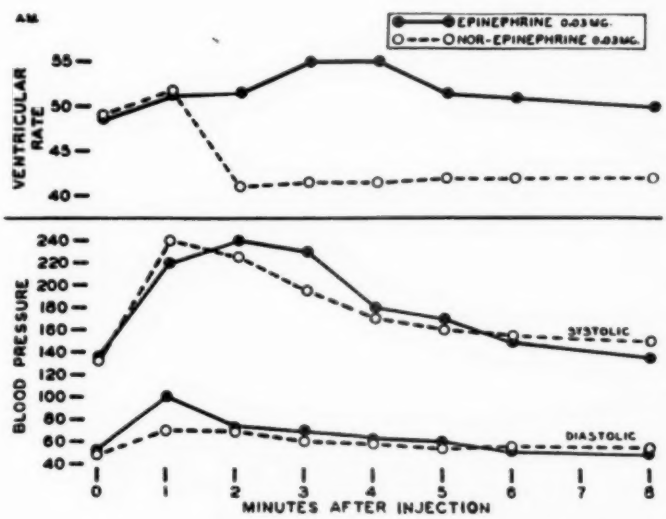

Fig. 3.—Patient A. M. Blood pressure and ventricular rate following the intravenous administration of 0.03 mg. of nor-epinephrine hydrochloride and 0.03 mg. of epinephrine hydrochloride. Note the slight transient rise and subsequent drop in the ventricular rate following nor-epinephrine and the sustained increase in rate following epinephrine.

observations of Goldenberg and associates,[7] who found no significant cardiac stimulation by nor-epinephrine using the cardiac catheterization method, while epinephrine consistently increased cardiac output. The absence of a cardiac stimulant action by nor-epinephrine should renew interest in the possible role of hyperactivity of the sympathetic nervous system or of abnormal metabolism of a sympathomimetic pressor substance in the genesis of hypertension. Since clinical hypertension is not associated with an increased cardiac output, it has been difficult to implicate increased sympathetic nervous activity as long as epinephrine was the only known sympathetic transmitter. The presence in the body of a potent sympathomimetic pressor agent (nor-epinephrine) having little or no cardiac stimulating action provides a possible basis for participation of the sympathetic nervous system in the genesis of essential hypertension.

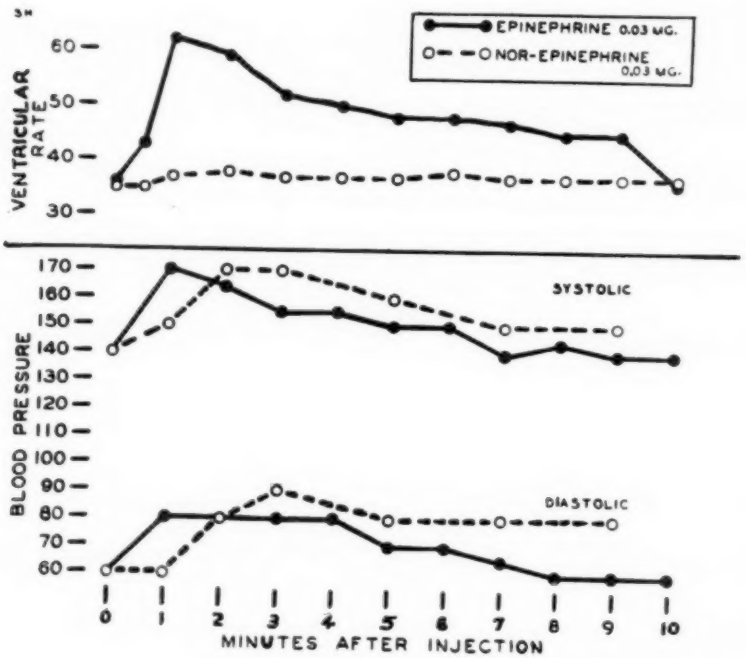

Fig. 4.—Patient S. H. Blood pressure and ventricular rate after the intravenous administration of nor-epinephrine hydrochloride and synthetic l-epinephrine bitartrate. Note the absence of response of the ventricular rate to a pressor dose of nor-epinephrine as compared with the marked and sustained increase in rate following epinephrine.

The introduction of a new sympathomimetic compound requires an evaluation of its place in practical therapeutics and particularly an estimation of its therapeutic activity as compared with that of epinephrine. In cardiac treatment, the chief application of the sympathomimetic compounds is in the therapy and prevention of sudden cardiac arrest such as may occur in heart block. The present studies show that nor-epinephrine has little or no cardiac stimulating action and thus the compound is not applicable to the treatment of cardiac standstill.

Goldenberg and his associates[9] recently reported on the use of nor-epinephrine as a pressor drug in certain hypotensive states. Although these observers do not suggest this compound in the shock associated with coronary occlusion, they do refer to experiments in dogs which show consistent increases in coronary flow following the intravenous administration of nor-epinephrine. Since the observations of Goldenberg and associates[7] and the present studies indicate that nor-epinephrine has little or no cardiac stimulating action, it might be considered a very desirable pressor drug in the treatment of the shock of coronary occlusion.

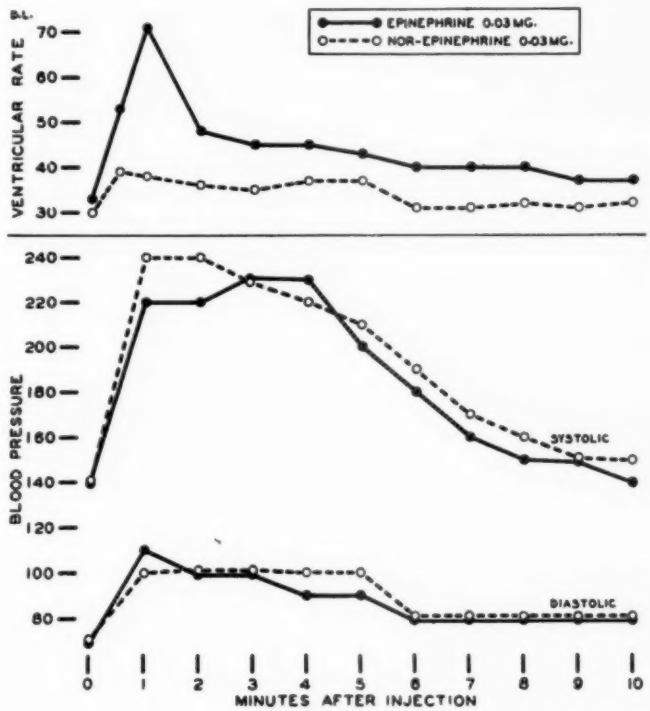

Fig. 5.—Patient D. L. This shows the marked and sustained increase in the ventricular rate following the intravenous administration of synthetic levo-epinephrine and the slight reaction following the administration of nor-epinephrine.

However, it has been shown by Garb and Chenoweth[10] that in the experimental animal, in which the heart has been sensitized by hydrocarbon inhalation, nor-epinephrine consistently induces the serious and usually fatal arrhythmia, ventricular fibrillation. Since the ischemic myocardium is also predisposed to this serious arrhythmia, it would appear that there might be a definite hazard in the administration of this compound in conditions in which the coronary circulation is inadequate.

CONCLUSIONS

The effects of nor-epinephrine and of epinephrine on the ventricular rate have been studied in ten patients with complete heart block.

In doses which produce a definite pressor effect, nor-epinephrine shows a minimal and transient response while epinephrine produces a marked and sustained increase in the ventricular rate.

Nor-epinephrine is of no value in therapy for the prevention or treatment of cardiac standstill.

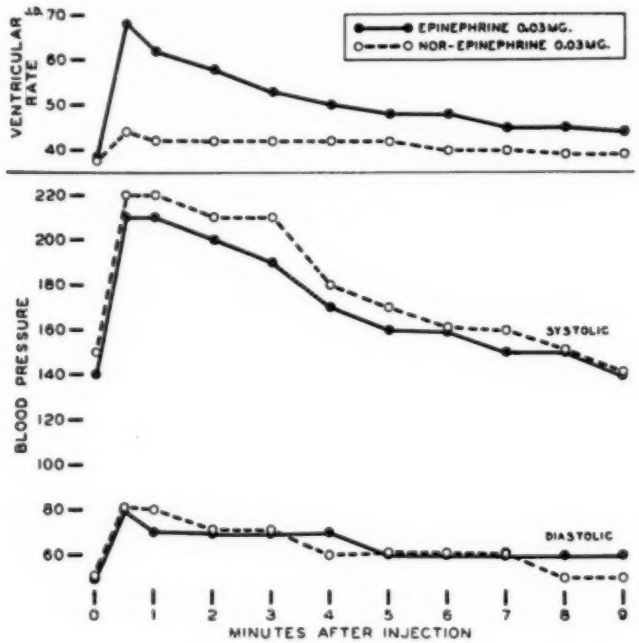

Fig. 6.—Patient J. D. The injection of epinephrine is followed by a marked increase in the ventricular rate. Nor-epinephrine produces a very slight effect on the ventricular rate. The pressor reaction is somewhat greater following the administration of nor-epinephrine.

The minimal cardiac action of nor-epinephrine suggests its use as a pressor agent in hypotensive states. However, there is evidence that this compound induces ventricular fibrillation in the sensitized myocardium, and this indicates a possible hazard in the administration of nor-epinephrine in conditions in which myocardial ischemia is present.

We are indebted to Dr. Gordon A. Alles of Pasadena, Calif., for the supply of levo-nor-epinephrine and to the Sterling-Winthrop Research Institute of Rensselaer, N. Y., for the synthetic levo-epinephrine.

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A PROLONGED STUDY OF ORAL VERATRUM VIRIDE IN THE TREATMENT OF ESSENTIAL HYPERTENSION

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ALTHOUGH veratrum viride has been known for many years to be a very potent hypotensive agent,[1-4] particularly when given parenterally, comparatively little interest has been shown in it for prolonged oral administration. This was due not only to the uncertainty and irregularity of action but also to the short duration and poor standardization of the older preparations which were available.

Recently, Freis and his co-workers reported very good results with a new standardized preparation of veratrum viride (Vertavis*) which is made in tablet form and has a duration of action from two to ten or fourteen hours.[5,6] We had been investigating the effects of a liquid preparation of veratrum viride intravenously and were impressed by the very marked and sudden hypotensive effect of this drug which, however, was of only short duration.[8] It was, therefore, with great enthusiasm that we decided to make a study of essential hypertensives using this new preparation to see if we could obtain equally good results.

The drug used was Vertavis, which is a mixture of the whole powdered alkaloids of veratrum viride made in coated tablets with 10 Craw units to the tablet. In order to evaluate the effect of the drug without bias, placebo tablets were used which had the identical appearance of the active drug, and these were substituted for the drug at irregular intervals. Patients who were on a special diet or were taking sedatives at the beginning of the study were continued on this therapy during veratrum administration.

The study was conducted at the Los Angeles County Hospital, and the patients studied were regular visitors at various clinics in this hospital. They had been previously studied carefully to confirm the diagnosis of essential hypertension. They were unselected, except that they might be classified as the more resistant type of case, as the patients who responded well to the usual nonspecific methods of therapy were not referred to this clinic.

The patients originally comprised a group of twenty-eight, however one patient was dropped from the study because the blood pressure was considered too low, and five patients stopped attending the clinic before treatment was begun. The remaining twenty-two patients who comprise this study all had blood pressures above 175 mm. Hg systolic and above 100 mm. Hg diastolic. The average age for the group was 53 years, the youngest being 32 and the oldest 86 years.

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Presented by title at the Western Society of Clinical Research, Salt Lake City, January, 1950.

Received for publication May 18, 1950.

*Irwin Neisler and Company, Decatur, Ill., who generously supplied the Vertavis and placebo tablets used in this study.

There were fourteen female and eight male patients, of whom twelve were white and ten Negro. The average known duration of hypertension was nine years for the group, the shortest being six months and the longest thirty years. It was felt that this comprises a group of the type of patients so frequently seen in the office daily and for whom thus far we have had so little to offer in the form of specific medical therapy.

In order to minimize the psychic effect upon the patients' blood pressures or possible variations in observations, the following method was followed. The patients were seen weekly, and all of the blood pressures were taken and recorded by one observer. The patients were ushered into the clinic room, and a blood pressure and pulse were taken immediately and recorded with the patient sitting. The patient was then allowed to lie quietly on a comfortable examining table with curtains drawn between all patients. Noise was kept at a minimum in order to allow the patients adequate relaxation. After ten to fifteen minutes resting the blood pressure and pulse were again taken and recorded. To avoid possible variations in blood pressure between the two arms, the left arm was used on all patients for all readings. After recording the blood pressure in the prone position, the patient's chart was consulted, and it was then decided whether the next supply of tablets would be placebo or veratrum. The patients were given only a sufficient supply of tablets to last until the next visit. In order to be sure which type of tablet a patient was taking at a particular visit, he was instructed either to return any left-over tablets or to take them before starting on the next supply. Throughout the study different patients were shifted from one type of tablet to the other at different times. By this method the observer could not know at the time of taking the readings whether the patient had been taking the veratrum or placebo during the preceding week. Also, as the patients did not know that placebos were being used, any undesirable effect from suggestion was diminished for both the observer and the patient. Neither were the blood pressures told to the patient, although the patients were encouraged to believe they were improving in order to secure cooperation in attendance.

The patients were usually started on 20 units daily, one tablet in the morning on arising and the other at the evening meal. The observations were made at the clinic approximately three to six hours after the morning dose. The dose was rapidly increased to the patient's tolerance, which was the maximum amount the patient could take without having more than slight nausea. The daily maximum dose varied from 60 to 120 units, or 6 to 12 tablets, and averaged 82 units per patient for the group. The maintenance dose was about 20 units less as symptoms were produced with the maximum amount.

No attempt was made to determine whether a hypotensive response was obtained until the study was near completion. At this time a rapid survey of the data suggested that the changes in blood pressure were probably not great, so the study was discontinued. The period of observation for different patients varied between two and five months.

The results were then summarized and tabulated in the following manner in order to compare the numerous recordings. The blood pressure and pulse recordings, sitting and lying, were averaged for each visit for each patient; the

TABLE I.

PATIENT	SEX	AGE	WITHOUT TREATMENT OR WITH PLACEBO			WITH TREATMENT			DIFFERENCE WITH AND WITHOUT TREATMENT		MAX. DOSE (UNITS)	SYMPTOMATIC IMPROVEMENT
			NO. VISITS	AVERAGE BLOOD PRESSURE	AVERAGE PULSE	NO. VISITS	AVERAGE BLOOD PRESSURE	AVERAGE PULSE	BLOOD PRESSURE	PULSE		
F.S.	F	45	6	219/142	79	8	217/134	80	− 2/−8	+ 1	100	None
A.L.	M	66	7	249/133	104	16	236/123	91	−13/−10	−13	80	Slight
O.O.	F	51	8	198/122	72	6	204/120	67	+ 6/−2	− 5	60	None
M.T.	F	38	8	183/114	69	4	170/115	67	−13/+1	− 2	80	Much
H.F.	M	56	10	184/111	67	4	174/104	65	−10/−7	− 2	100	None
T.J.	F	38	9	211/131	77	3	206/120	69	− 5/−11	− 8	60	Much
J.M.	F	42	10	208/117	104	7	214/117	106	+ 6/0	+ 2	80	Slight
G.M.	F	58	9	220/121	89	5	208/116	79	−12/−5	−10	100	None
V.W.	F	52	7	197/105	69	4	206/106	59	+ 9/+1	−10	100	None
H.A.	M	72	7	199/122	56	11	208/108	50	+ 9/−14	− 6	120	Slight
P.M.	F	32	7	222/124	78	8	209/120	72	−13/−4	− 6	60	None
M.S.	F	56	6	235/123	102	11	225/115	96	−10/−8	− 6	100	Much
V.S.	M	36	5	179/132	77	7	172/125	81	− 7/−7	+ 4	80	Slight
O.D.	F	57	6	238/109	86	6	240/105	79	+ 2/−4	− 7	70	None
M.B.	F	49	6	194/103	78	8	168/93	79	−16/−10	+ 1	80	None
F.T.	F	60	5	217/111	75	4	207/101	70	−10/−10	− 5	80	Much
H.K.	M	86	7	282/123	75	7	266/115	74	−16/−8	− 1	60	Slight
E.F.	F	43	3	223/115	63	4	214/113	77	− 9/−2	+14	80	Worse
F.O.	M	63	2	218/132	81	4	201/119	76	−17/−13	− 5	60	None
B.G.	F	52	3	184/112	70	10	159/98	67	−25/−14	− 3	80	None
R.D.	M	45	4	203/127	72	8	198/121	64	− 5/−6	− 8	100	Much
E.W.	M	65	4	183/108	83	8	170/103	87	−13/−5	+ 4	80	Much

systolic and diastolic recordings were averaged separately. These recordings were considered to be the average pressure and pulse for that patient on that particular visit. Next, all of the average blood pressures and pulse rates for a patient not on treatment or while taking placebo were averaged together in the same way. The average blood pressure and pulse rate were then secured for the patient while taking veratrum, and these averages were tabulated as shown in Table I. The differences in blood pressure and pulse rate are listed as plus or minus to indicate whether there was an increase or decrease while receiving treatment. After tabulation of these data they were submitted to a statistician for analysis.

RESULTS

From Table I it can be seen, on comparing the average blood pressure untreated and with placebo tablets with the average blood pressure with veratrum, that sixteen of the twenty-two patients showed a drop in both systolic and diastolic pressure. Three patients showed a drop in diastolic pressure and a fall in systolic pressure, and two patients showed a rise in both systolic and diastolic pressures. The average overall change (comparing the averages of all patients) showed a fall of 7 mm. Hg in the systolic and 6.6 mm. Hg in the diastolic blood pressure. Considering both systolic and diastolic pressures together, the poorest result was in a patient whose systolic pressure rose 9 mm. Hg and whose diastolic pressure fell 25 mm. Hg and 14 mm. Hg, respectively.

On comparing the average pulse rate before and during treatment, the overall change showed a drop of 3 beats. Sixteen patients' pulse rates fell with treatment; five patients' pulse rates rose. The range was a fall of 13 to a rise of 14 beats.

Symptomatically, six patients claimed they felt much improved; five felt slightly improved; ten felt unchanged; and one felt worse with treatment.

Looking at these results from a slightly different point of view, from a survey of the observations of blood pressure in different categories rather than from a comparison of patients, we can test the significance of our results (Table II).

TABLE II.

	SITTING	LYING
Untreated Blood Pressure		
Observations	114	98
Mean	214/122	209/122
Range	150–298/95–160	110–296/94–150
Placebo Blood Pressure		
Observations	23	23
Mean	209/114	207/114
Range	164–284/98–135	166–264/96–135
Treated With Veratrum		
Observations	153	150
Mean	199/113	204/114
Range	128–300/74–144	140–280/85–145

The only appreciable fall, as demonstrated by a comparison of these means, is in the systolic sitting pressure, before and during treatment, of fifteen points. The blood pressure records taken in the lying position certainly do not seem to show a tendency to be lower than in the sitting position.

TABLE III. FREQUENCY DISTRIBUTION: UNTREATED SYSTOLIC BLOOD PRESSURE RECORDINGS, (EXCLUDING PLACEBO OBSERVATIONS) ON 22 PATIENTS, SITTING

RANGE OF BLOOD PRESSURE (MM. HG)	NO. OBSERVATIONS	BLOOD PRESSURE IN WORKING UNITS	COLUMNS (2) × (3)	COLUMNS (3) × (4)
150 – 154	2	−14	−28	392
155 – 159	0	−13		
160 – 164	3	−12	−36	432
165 – 169	0	−11		
170 – 174	7	−10	−70	700
175 – 179	3	− 9	−27	243
180 – 184	6	− 8	−48	384
185 – 189	3	− 7	−21	147
190 – 194	15	− 6	−90	540
195 – 199	4	− 5	−20	100
200 – 204	9	− 4	−36	144
205 – 209	5	− 3	−15	45
210 – 214	5	− 2	−10	20
215 – 219	7	− 1	− 7	7
220 – 224	10	0		
225 – 229	2	+ 1	+ 2	2
230 – 234	6	+ 2	+12	24
235 – 239	3	+ 3	+ 9	27
240 – 244	3	+ 4	+12	48
245 – 249	4	+ 5	+20	100
250 – 254	6	+ 6	+36	216
255 – 259	3	+ 7	+21	147
260 – 264	2	+ 8	+16	128
265 – 269	0	+ 9		
270 – 274	0	+10		
275 – 279	2	+11	+22	242
280 – 284	0	+12		
285 – 289	1	+13	+13	169
290 – 294	1	+14	+14	196
295 – 299	2	+15	+15	450
Totals	114	+ 1	−201	4,903

Mean in working units (−201 + 114) = −1.763.
Mean in real units (222.5 −5[1.763]) = 213.7 mm. Hg.
Mean squared deviation in working units round 0 = 4903/114 = 43.009.
Therefore: Standard deviation in working units is (square root $43.009-1.763^2$) = 6.32.
Standard deviation in real units (6.32 × 5) = 31.6.

Is the fall of fifteen points in systolic pressure significant? We would not think so because: (a) under veratrum, the systolic blood pressure was five points higher when the patient is lying than when he is sitting; and a comparison of systolic blood pressures with the patient lying, before and after treatment, showed a drop of only five points; (b) there was a great variation in the systolic blood pressure before treatment; almost every patient showed a change, both up and down, of 30 to 40 points, and one even showed a change of 80 points; (c) the standard deviation of the group of untreated systolic blood pressure records, with the patient sitting, was 31.6, which is extraordinarily high, indicating a

great variability. A fall of 15 points would not even indicate the usual amount of change that one might expect in this group. (See Table III for the frequency distribution.)

Is a fall of 9 points in the diastolic pressure significant? Again we would not think so because: (a) again there is a great variation, even in this more stable pressure, before treatment; a shift of 20 points is not unusual; (b) the standard deviation of the group of untreated diastolic blood pressure records, with the patient sitting, was 13.54, which is still quite a high figure, indicating a considerable inherent variation in the observations; thus a fall of 9 points would be entirely a change which one could expect, even before treatment. (See Table IV for the frequency distribution.)

TABLE IV. FREQUENCY DISTRIBUTION: UNTREATED DIASTOLIC BLOOD PRESSURE RECORDINGS (EXCLUDING PLACEBO OBSERVATIONS) ON 22 PATIENTS, SITTING

RANGE OF BLOOD PRESSURE (MM. HG)	NO. OBSERVATIONS	BLOOD PRESSURE IN WORKING UNITS	COLUMNS (2) × (3)	COLUMNS (3) × (4)
95 – 99	1	−5	− 5	25
100 – 104	16	−4	−64	256
105 – 109	6	−3	−18	54
110 – 114	14	−2	−28	56
115 – 119	14	−1	−14	14
120 – 124	27	0		
125 – 129	7	+1	+ 7	7
130 – 134	15	+2	+30	60
135 – 139	2	+3	+ 6	18
140 – 144	5	+4	+20	80
145 – 149	2	+5	+10	50
150 – 154	3	+6	+18	108
155 – 159	1	+7	+ 7	49
160 – 164	1	+8	+ 8	64
Totals	114	+3	−23	841

Mean in working units (−23/114) = −.202.
Mean in real units (122.5–5[.202]) = 121.5 mm. Hg.
Mean squared deviation in working units round 0 = 841/114 = 7.377.
Therefore: Standard deviation in working units is (square root $7.377-.202^2$) = 2.708.
Standard deviation in real units (2.708 × 5) = 13.54.

The same line of reasoning can be applied to the other groups, since the blood pressures taken in the lying position seem to vary just as much as those in the sitting position. The number of observations under placebo treatment are too few to be significant, but the mean readings of these groups are within 10 points of both the untreated and treated groups, and thus do not show any clear trend.

Since our results failed to show any significant response, the question naturally arises as to why they were so inferior to those reported by Freis. This is not clear. However, it could not be due to using smaller doses of the drug. Freis states that the therapeutic dose varied between 10 and 40 Craw units and that if it were increased beyond this point there resulted further reduction of blood pressure, but also toxic reactions. His patients were maintained on from 30 to 80 units per day. Our patients tolerated somewhat larger doses, the main-

tenance dose being from 40 to 100 units per day, and the average for the group was 62 units. Five patients were able to tolerate 100 units daily with only two of these complaining of occasional slight discomfort.

Objection may be raised to the manner of obtaining the average blood pressure during treatment. It might be said that since the blood pressure is lowered only at a critical level of dosage, all other readings taken with smaller dosage should be excluded or should be included with the control readings. This possibility was not considered originally, and they were grouped in this way in order to have as many readings as possible in each group so that when averaged together unusual fluctuations would not too greatly affect the results obtained. When this thought came up we went back over the original data but could detect no differences in the readings that could be correlated with dosage. In fact quite often the blood pressure was higher with the maximum dose than the following week when the patient was on placebo. Fig. 1 is a graphic record of a typical patient.

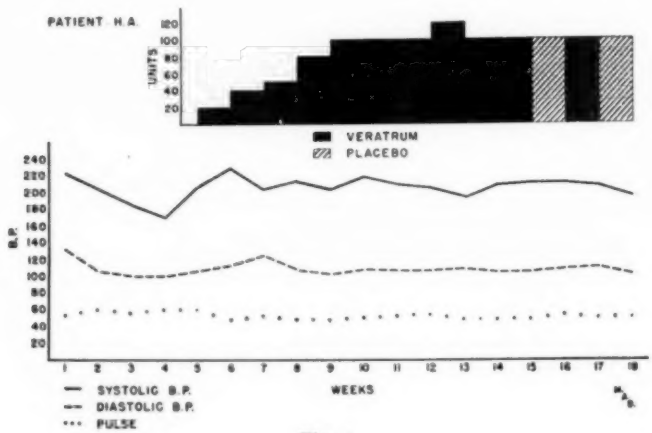

Fig. 1.

The possibility of poor absorption of the tablets was also considered, but when the same drug was given to hospitalized patients for a short time a definite hypotensive effect was obtained in some of them.[7] This latter group of patients has not yet been studied thoroughly enough to reach any definite conclusions; however, there is indication that the drug is fairly well absorbed and also that for at least a short time a hypotensive effect may be obtained. Therefore, although we cannot explain our results in this study, a possible explanation may be the phenomenon of tachyphylaxis. Krayer found when using a more purified preparation (protoveratrine) in dogs, that this phenomenon developed rapidly.[8]

Our conclusion, therefore, is that veratrum viride in the form used did not show any significant hypotensive effect in essential hypertension over a prolonged period, but should be further investigated, particularly in acute conditions.

SUMMARY

1. A group of twenty-two patients with essential hypertension was treated with veratrum viride in tablet form for periods varying from two to five months.

Each patient was given the maximum dose he could tolerate and was used as his own control by substituting placebos for the drug.

2. Statistical analysis of the results obtained failed to show a significant change in blood pressure or pulse rate while under treatment.

3. Tachyphylaxis is suggested as the possible reason for the results obtained.

The authors wish to express their appreciation to Mrs. Mary Cosby for the statistical analyses in this paper.

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ABNORMAL BALLISTOCARDIOGRAPHIC PATTERNS IN CARDIOVASCULAR DISEASE AS RECORDED WITH THE LOW-FREQUENCY, CRITICALLY-DAMPED BALLISTOCARDIOGRAPH

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USING a high frequency ballistocardiograph, Starr[1,2] has shown that certain abnormal patterns are associated with cardiac disease and that there is an improvement in the pattern of those individuals to whom digitalis is administered. In the present study of pattern abnormalities in disease, the low-frequency, critically-damped ballistocardiograph designed by Nickerson and Curtis[3] has been used because of the belief that it is a superior instrument.[4,5] It has been calibrated by Nickerson, Warren, and Brannon[4] against the method according to the Fick principle, using atrial catheterization. We have attempted to study the patterns qualitatively with the idea of (1) correlating pattern type with specific disease processes, and (2) correlating changes in a series of records with variations in clinical condition following treatment. As an example, we refer to the observations made in patients with coarctation of the aorta, in whom the pattern changes from an abnormal to a normal type after surgical removal of the constricted portion of the vessel.[6]

MATERIAL AND METHODS

The sixteen cases studied were hospital and clinic patients, including four with coronary heart disease; three with cor pulmonale secondary to pulmonary emphysema and fibrosis, two of whom also had coronary sclerosis; three with hyperthyroidism; two with hypertension; two with rheumatic heart disease; and two having severe anemia with cardiac failure. Evidence of heart failure was present in twelve patients; two gave history of paroxysmal nocturnal dyspnea; and in two there was no evidence of cardiac decompensation.

Observations were made every two or three days for a period of three to six weeks, with a follow-up study of six weeks to ten months. The observations consisted of the recording of ballistocardiographic patterns, calculation of cardiac output, determinations of blood volume using the blue dye T-1824,[7] venous pressure, circulation time with Decholin,* vital capacity, recording of electrocar-

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This investigation was supported in part by a grant from the Division of Research Grants and Fellowships of the National Institute of Health, U. S. Public Health Service, and in part by a contract between the Medical Research and Development Board, Department of the Army and Columbia University.

Received for publication June 7, 1950.

*Supplied through the courtesy of Ames Company, Inc., Elkhart, Ind.

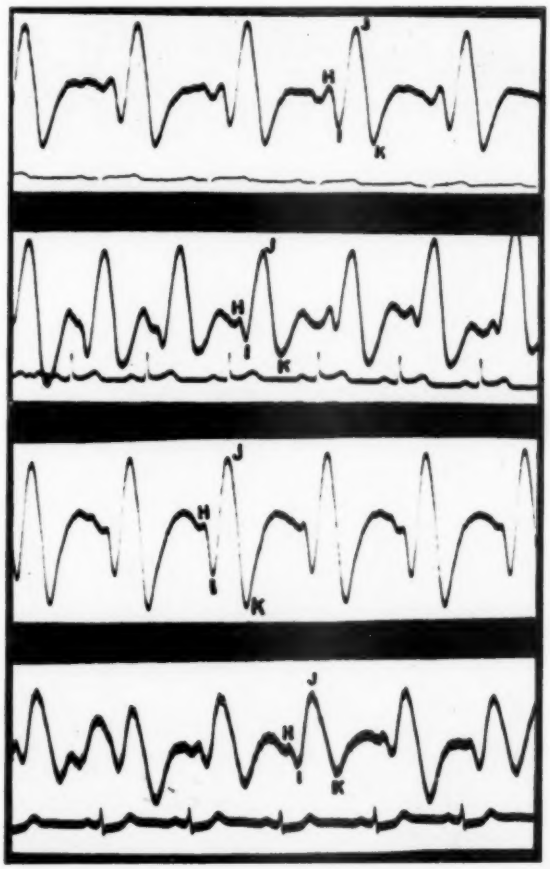

Fig. 1.—The ballistocardiograms of four normal individuals are shown. The *H*, *I*, *J*, and *K* peaks are indicated.

diographic tracings, determination of blood pressure, heart rate, changes in weight, and variations in the size of the heart, using the two-meter x-ray film of the chest.

Patients were studied in the basal state. The ballistocardiographic tracings were made after thirty minutes of rest in the recumbent position and were followed by estimation of blood volume and the other determinations. The cardiac output was determined both during normal respiration and with breath holding. Routine therapy consisted of bed rest for the hospitalized cases, low-sodium diet, and digitalization (except in two cases) without the use of diuretics and without attempting to force fluids. Antianemic and antithyroid therapy were administered when indicated.

RESULTS

Normals (Fig. 1).—The records of four normal individuals are shown for comparison with those obtained in states of disease.

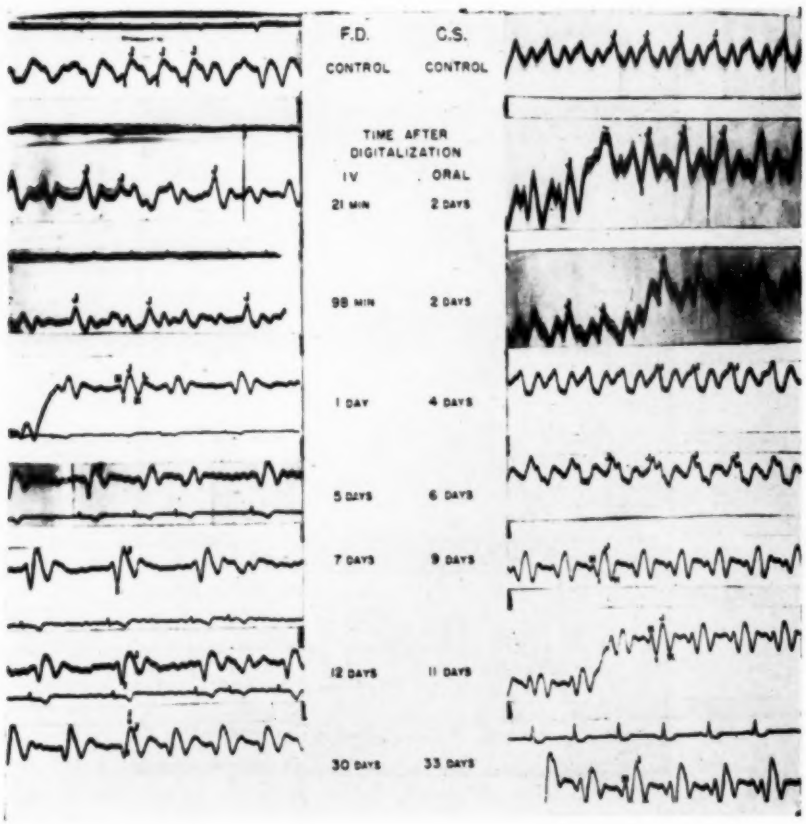

Fig. 2.—F. D. and C. S.

F. D. was a 51-year-old Negro man. The diagnosis was coronary sclerosis and cardiac failure. The electrocardiogram was abnormal and showed the digitalis effect with treatment. The heart decreased in size but continued to show left-sided enlargement. The patient was given an intravenous injection of 1.6 mg. Lanatoside "C" followed by 0.2 mg. digitoxin orally daily. There was immediate clinical improvement and compensation was maintained. The ballistocardiographic record shows a corresponding improvement in the pattern.

C. S. was a 62-year-old white man. The diagnosis was coronary sclerosis, pulmonary fibrosis, and emphysema with cor pulmonale and cardiac failure. The electrocardiogram was abnormal and showed the digitalis effect with treatment. The heart decreased somewhat in size but remained larger than normal. The patient was digitalized orally with 1.8 mg. digitoxin and maintained by 0.2 mg. digitoxin orally daily. He showed continued improvement in the clinical state and in the ballistocardiographic records.

Fig. 3.—M. H., J. B., and W. C.

M. H. was a 61-year-old Negro man. The diagnosis was coronary sclerosis, anginal pain, and a healed anterior myocardial infarct. Infarction had occurred seven months prior to this study. The electrocardiogram was normal, and the only effect of digitalis was a marked slowing of the heart rate. The heart was normal in size.

A, Control.

B, Twenty-five minutes after start of intravenous injection of 1.6 mg. Lanatoside "C".

C, Seventy minutes after start of the injection.

D, Eleven days after digitalization. The patient was being maintained on 0.2 mg. digitoxin orally daily.

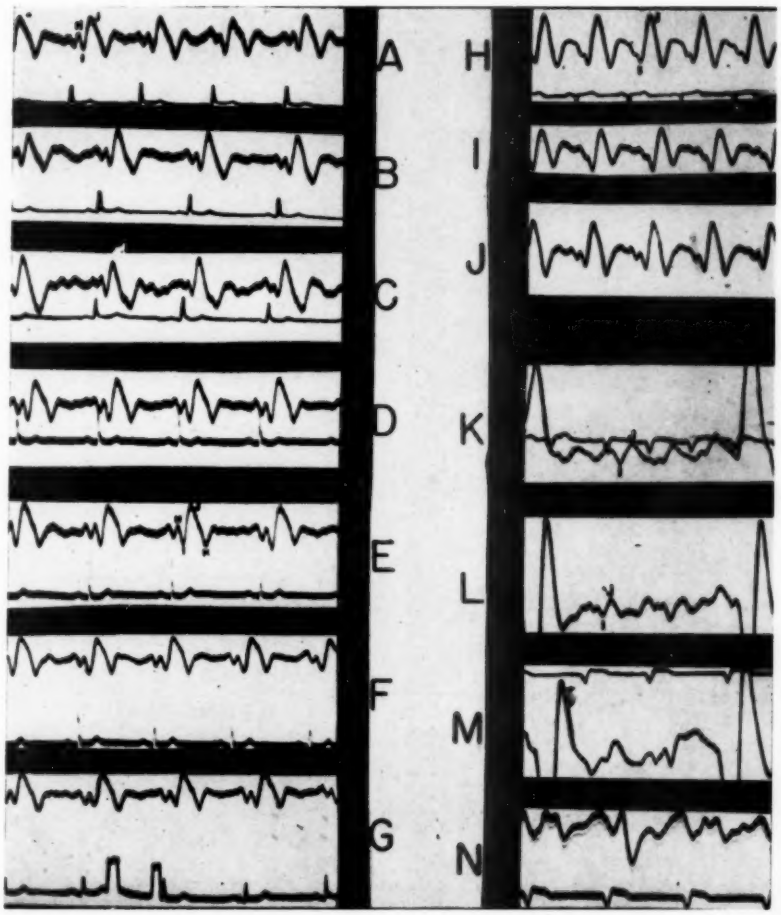

Fig. 3.—(*See opposite page for beginning of legend.*)

E, Twenty-one days after digitalization, last day of maintenance dosage.

F, Twenty-one days after discontinuing digitoxin.

G, Thirty days after discontinuing digitoxin and four days prior to second coronary occlusion and death.

J. B. was a 58-year-old white man. The diagnosis was coronary sclerosis, a healed anterior myocardial infarct. Infarction had occurred eight weeks prior to study and ventricular tachycardia twenty-five days prior to study. The arrhythmia was abolished by quinidine. Edema of scrotum and sacrum appeared five days prior to study. The abnormal electrocardiogram and slightly enlarged heart were unaffected by therapy.

H, Control.

I, Seven days after digitalization with 1.6 mg. digitoxin orally in divided doses, and maintenance dosage of 0.2 mg. orally daily.

J, Five months after initial digitalization; continued maintenance dosage.

W. C. was a 72-year-old white man. The diagnosis was coronary sclerosis and severe cardiac failure. The electrocardiogram showed left bundle branch block, and the x-ray an enlarged heart. Neither showed any change during the period of study.

K, Control. After this record 1.4 mg. Lanatoside "C" were given intravenously. The following day an additional 0.6 mg. digitoxin was given orally, and he was maintained on 0.2 mg. orally daily.

L, Seven days after digitalization. The patient's clinical condition was slightly improved.

M, Twenty days after digitalization. The patient's clinical condition was becoming worse.

N, Forty-five days after digitalization. The patient's condition was definitely worse; he died suddenly seven hours after this record was made.

The large excursions noted in records *K*, *L*, and *M* are due to exaggerated respiratory effort.

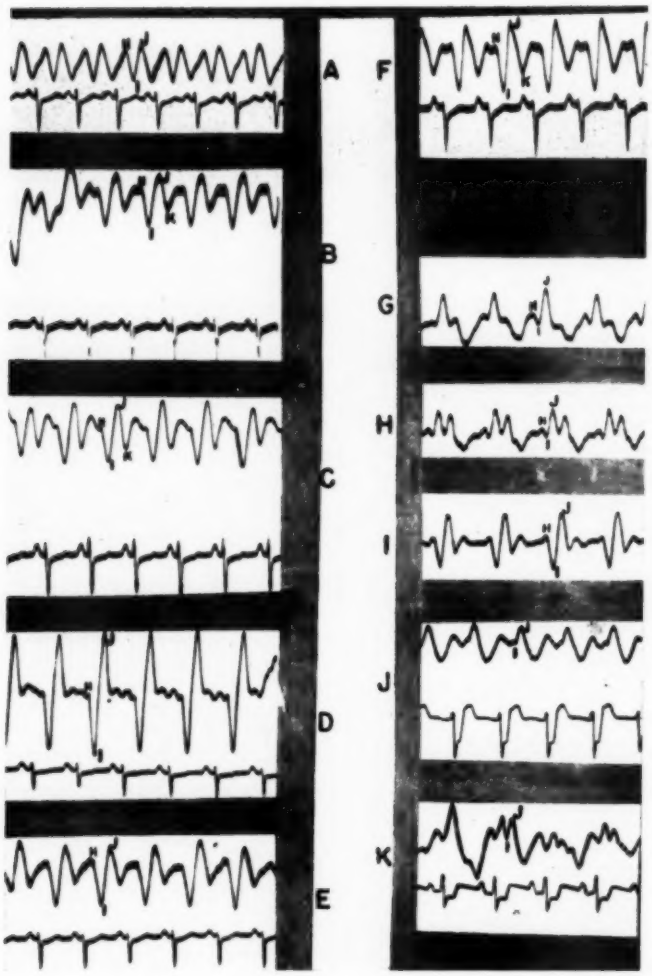

Fig. 4.—L. W. and J. K.

L. W. was a 56-year-old white man. The diagnosis was pulmonary emphysema and fibrosis, cor pulmonale, and cardiac failure. The electrocardiogram was abnormal and showed the digitalis effect with treatment. The heart decreased in size with therapy, only to increase when the therapy was discontinued and remain the same size when the therapy with digitoxin was reinstituted.

A, Control.

B, Two days after digitalization with 1.6 mg. digitoxin orally in divided doses, and a maintenance dosage of 0.2 mg. digitoxin orally daily.

C, Three days after digitalization.

D, Two weeks after digitalization. Marked improvement with only minimal signs of cardiac insufficiency.

E, Six weeks after the patient discontinued digitoxin. Clinical evidence of congestive failure reappeared.

F, One month after digitoxin therapy was reinstituted with partial relief of congestive failure.

J. K. was a 60-year-old white man. The diagnosis was coronary sclerosis, pulmonary emphysema, and fibrosis with cor pulmonale and cardiac failure. The electrocardiogram was abnormal and showed the digitalis effect with therapy. When he returned in cardiac failure, right bundle branch block was present and persisted. The heart showed a slight decrease in size with therapy and was still smaller when the patient returned in failure.

G, Control.

(*Legend continued on next page.*)

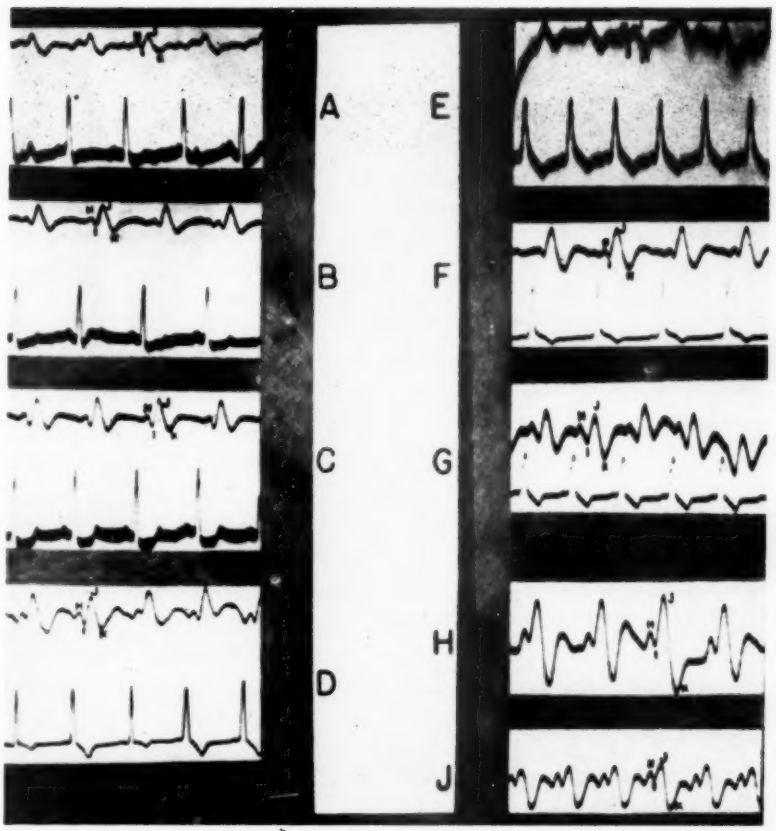

Fig. 5.—H. S. and H. M.

H. S. was a 35-year-old Negro man. The diagnosis was hypertensive cardiovascular disease with minimal evidence of congestive failure. The electrocardiogram was abnormal but improved with treatment. Following the first stage of thoracolumbar sympathectomy, the electrocardiogram became abnormal again. The lung fields cleared under therapy, and the heart decreased in size.

A, Control.

B, One minute after 1.6 mg. Lanatoside "C" intravenously.

C, One day later. The maintenance dosage was 0.2 mg. digitoxin orally daily.

D, Twenty-one days post first stage thoracolumbar sympathectomy.

E, No digitalis for six weeks. After this record, 1.6 mg. Lanatoside "C" was administered intravenously and a maintenance dose of 0.2 mg. digitoxin was given orally daily.

F, One day later.

G, Twenty-one days post second stage sympathectomy.

H. M. was a 32-year-old Negro man. The diagnosis was hypertensive cardiovascular disease with minimal evidence of congestive failure. The electrocardiogram was abnormal, and the heart was enlarged. There was no follow-up of either test.

H, Control. Following this record he received 1.6 mg. digitoxin orally and a maintenance dose of 0.2 mg. digitoxin orally daily.

J, Post first stage thoracolumbar sympathectomy.

H, Five days after oral digitalization with 1.6 mg. digitoxin and maintenance dosage of 0.2 mg. digitoxin orally daily.

I, Eleven days after the start of the therapy. The patient was recompensated.

J, Five months later. The patient returned, having discontinued digitoxin with recurrence of congestive failure.

K, Three days after ballistocardiogram *J*. There was slight clinical improvement.

Coronary Sclerosis.—Three of the four patients with coronary sclerosis (F.D. in Fig. 2, and M. H., J. B., W. C. in Fig. 3) showed definitely abnormal patterns which improved with treatment. M. H. was not in cardiac failure, but after the intravenous administration of Lanatoside "C" there was an immediate straightening of the previously bowed *JK* segment. W. C., who was in marked cardiac failure with only slight and temporary improvement, had a pattern that was grossly abnormal and paralleled the clinical course which also showed only temporary improvement. The fourth patient, J. B., with definite evidence of coronary heart disease, had a normal ballistocardiogram.

Cor Pulmonale.—All three patients with cor pulmonale (C. S. in Fig. 2, and Fig. 4) were in cardiac failure and had abnormal patterns without definite indentifying features. With the return of compensation, the ballistocardiogram returned toward normal, only to regress when cardiac failure returned with voluntary omission of therapy.

Hypertension (Fig. 5).—Although both patients had minimal signs of cardiac failure, in only one (H. S.) was the pattern abnormal, and this was true of all of its component parts. Patient H. M. had a normal control pattern which became abnormal following the first stage of thoracolumbar sympathectomy. The patient expired suddenly during the second stage of the operation.

Rheumatic Heart Disease (Fig. 6).—Both patients had abnormal control records with bowing of the *JK* segment. Immediate improvement was noted following the intravenous administration of Lanatoside "C." In patient A. K. further improvement was observed when, at the end of thirty days of maintenance doses of digitoxin, she was given an extra 0.2 mg. of digitoxin orally for four days. When M. R. voluntarily discontinued the oral use of digitoxin because of nausea, a regression of the pattern was observed with improvement when the drug was again taken.

Thyrotoxicosis (Fig. 7).—All three of these individuals had abnormal patterns. In two of them there was a reversion toward normal coincident with clinical improvement. In the third case the abnormal pattern, i. e., broadening of the *J* wave, was maintained. This we attribute to the underlying heart disease. All three of these patients had a high cardiac output, and while the *I* wave is prominent in E. S. and J. H., it is not abnormally so in L. P.

Anemia (Fig. 8).—Both individuals have large *H* waves in the control tracings. Patient T. J. also had a broadened *J* wave. When the anemia and cardiac failure were corrected, the pattern returned toward normal, and no clinical evidence of organic heart disease could be found in either individual.

DISCUSSION

This study was designed (1) to relate abnormal ballistocardiographic patterns with specific disease processes in the myocardium, and (2) to correlate changes in a series of records with variations in clinical condition following treatment. The first of these objectives has not been successful, for although a damaged myocardium produces, in general, an abnormal ballistocardiographic pattern, no definite correlation is apparent between specific disease entities and the

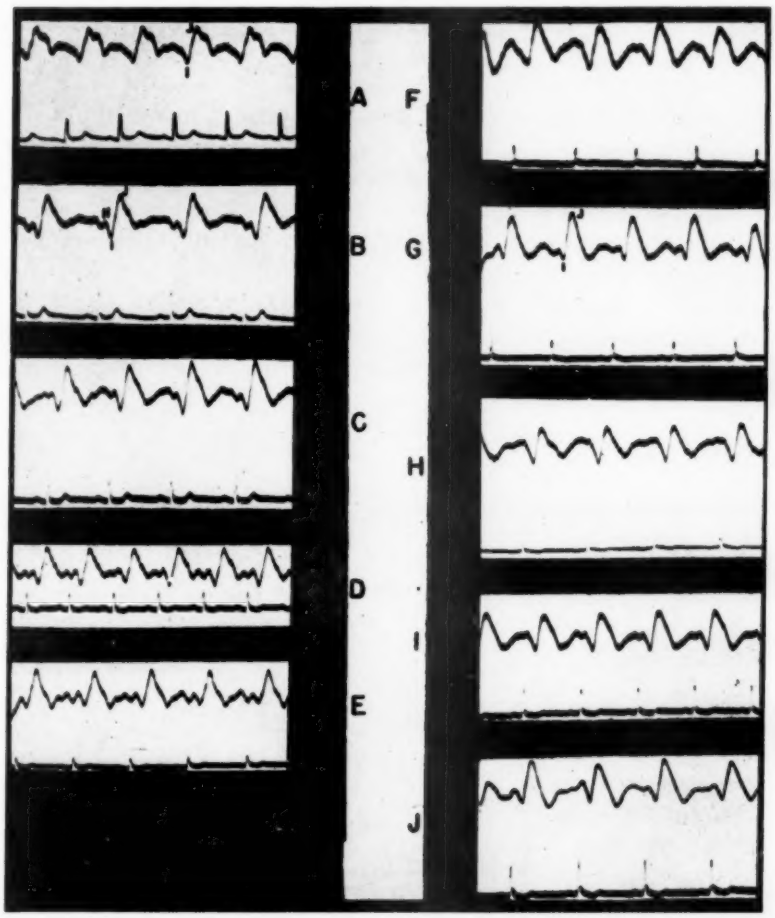

Fig. 6.—A. K. and M. R.

A. K. was a 38-year-old white woman. The diagnosis was inactive rheumatic heart disease, mitral stenosis and insufficiency, and occasional paroxysmal dyspnea. The control electrocardiogram was within normal limits. A tracing taken six hours after intravenous injection of Lanatoside "C" showed a slight increase in the amplitude of the T waves. A record taken one week later showed a diphasic T_2 and T_3. Increase in the dose of digitoxin augmented this effect. The mitral configuration of the heart remained unchanged with treatment.

A, Control.

B, One hour after injection of 1.4 mg. Lanatoside "C" intravenously. The ballistocardiographic pattern improved immediately.

C, Seven days later. The patient was being maintained on 0.2 mg. digitoxin orally daily.

D, Thirty-five days later. The maintenance dose was continued.

E, Thirty-nine days later. For the preceding four days the patient was on a maintenance dose of 0.4 mg. digitoxin orally daily.

M. R. was a 30-year-old white woman. The diagnosis was inactive rheumatic heart disease, mitral stenosis and insufficiency, and paroxysmal dyspnea. The electrocardiogram was normal and after therapy showed the digitalis effect. The mitral configuration of the heart remained unchanged with treatment.

F, Control.

G, One hour after injection of 1.6 mg. Lanatoside "C" intravenously. The change in the ballistocardiographic pattern became apparent immediately following injection.

H, Seven days after digitalization. The patient was being maintained on 0.2 mg. digitoxin orally daily.

I, Eight days after voluntarily discontinuing drug because of nausea.

J, Twenty-one days after returning to daily maintenance dosage of 0.1 mg. digitoxin orally daily.

mechanical functions of the heart as demonstrated by the ballistocardiographic pattern. Normal patterns are occasionally found in documented cases of myocardial disease. However, seriously diseased hearts usually show a pattern which is abnormal in all of its parts. The less diseased myocardium presents, in its earlier stages, a pattern in which the upward bowing of the *JK* segment is a common finding. We have found the latter abnormality present in 15 per cent of our series, comprising young and presumably normal individuals. Starr[8] has reported, in a follow-up study of a group of older individuals, that an abnormal ballistocardiographic pattern was the first clue to cardiac disease. At the present time we feel that pattern abnormalities are suggestive evidence of a diseased myocardium, regardless of etiology, but wish to emphasize that we are unable to substantiate the isolated finding of pattern abnormality as definite evidence of cardiac disease and suggest that the final decision should be based on clinical judgment.

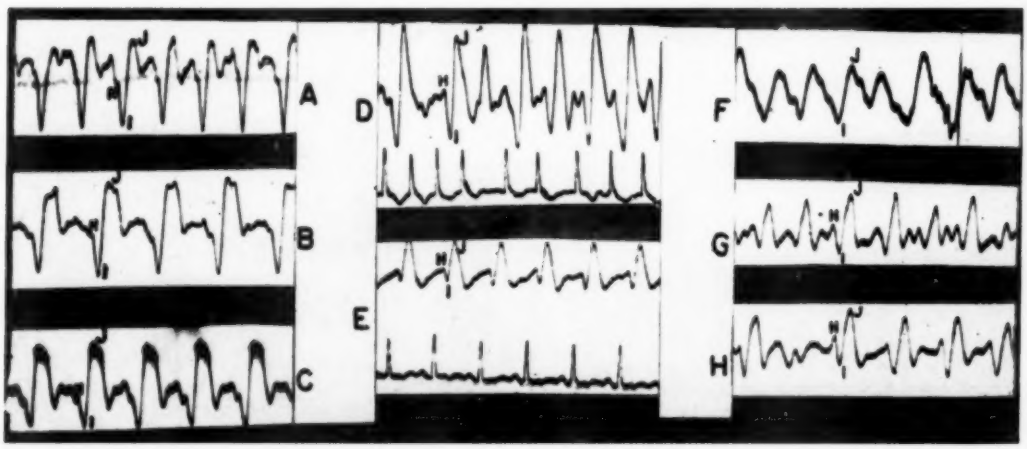

Fig. 7—E. S., J. H., and L. P.

E. S. was a 42-year-old Negro woman. The diagnosis was hyperthyroidism. She had recently been treated for cardiac decompensation but was now in compensated state. The electrocardiogram was abnormal and was unchanged by therapy. The treatment consisted of propylthiouracil and sodium iodide.

A, Two days after start of therapy.

B, Nine days later, showing clinical improvement.

C, Eighteen days later. Hyperthyroidism controlled, patient ready for thyroidectomy.

J. H. was a 45-year-old Negro woman. The diagnosis was hyperthyroidism and congestive failure. The electrocardiogram was abnormal but became normal, and the enlarged heart decreased to normal size with therapy. This consisted of potassium iodide, digitoxin, and propylthiouracil.

D, Eighteen hours after start of therapy.

E, Twelve days later. The patient showed improvement in cardiovascular status, but only slight improvement in hyperthyroidism.

L. P. was a 41-year-old white woman. The diagnosis was hyperthyroidism and congestive failure. The electrocardiogram was abnormal and after treatment showed the digitalis effect. The enlarged heart decreased in size with therapy and returned to a normal configuration. Therapy consisted of potassium iodide, propylthiouracil, and digitoxin.

F, Control. Therapy started after the record. 1.2 mg. digitoxin orally. Maintenance dosage was 0.2 mg. digitoxin orally daily.

G, Five days later. Both the cardiovascular and the hyperthyroid status improved.

H, Eight days later. Improvement continued. The patient became psychotic and was transferred to another institution.

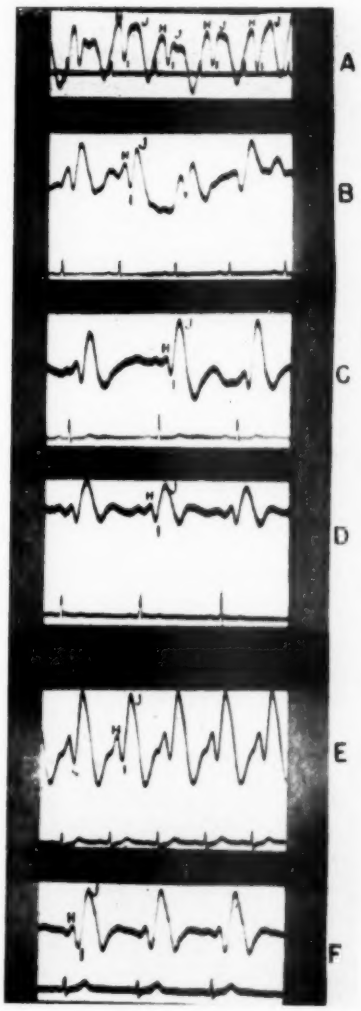

Fig. 8.—T. J. and M. W.

T. J. was a 35-year-old Negro woman. The diagnosis was primary and secondary anemia and cardiac failure. The abnormal electrocardiogram became normal with treatment. The enlarged heart decreased to normal size with therapy.

A, Control. The patient was then given 1.6 mg. digitoxin orally and maintained on 0.2 mg. digitoxin orally daily. She was also given transfusions and ferrous sulphate.

B. One day later.

C. Three days later. Vitamin B_{12} was administered.

D. Twenty-eight days later.

M. W. was a 31-year-old Negro woman. The diagnosis was secondary anemia and congestive failure. The control electrocardiogram was within normal limits and after restoration of normal red cell count there was an increase in amplitude of the T waves. The x-ray revealed an enlarged heart with straightening of the left border, decreasing to normal size and contour with therapy.

E, Control. The patient was given blood transfusions and ferrous sulphate but no digitoxin.

F, Eighteen days later. The anemia was corrected.

In pursuing the second objective, we were able to show that in those cases where clinical improvement in cardiac function was observed, there was an improvement of the ballistocardiographic tracing toward a normal pattern type. The individuals with the greatest clinical improvement showed the most marked improvement in pattern. In those cases where little clinical improvement with treatment was seen, there was correspondingly little improvement in the pattern. It was also evident in cases in which improvement was observed that if treatment was discontinued for some time, both the clinical picture and the pattern tended to revert to the original form. In only four patients did the electrocardiogram reflect improvement in the clinical state. In three, there was no demonstrable heart disease when the underlying cause of cardiac failure was successfully treated (two with anemia, one with hyperthyroidism). The fourth was a patient with hypertensive cardiovascular disease.

CONCLUSIONS

1. In most patients with myocardial disease there is a definite deviation of the ballistocardiographic pattern from that seen in normal, healthy individuals.
2. Pattern abnormality reflects mechanical dysfunction and not a specific etiology.
3. With changes in the degree of myocardial insufficiency there are parallel changes in the ballistocardiogram.
4. Records obtained with the low-frequency, critically-damped ballistocardiograph provide an objective method of evaluating therapy designed to improve the mechanical efficiency of the myocardium.

Acknowledgement is made to Mr. Vincent Glaviano and Mrs. Mary MacNamee for technical assistance.

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EXPERIMENTAL CHOLESTEROL ARTERIOSCLEROSIS
II. CHANGES PRODUCED IN GOLDEN HAMSTERS AND IN GUINEA PIGS

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IN 1946,[1] I reported briefly that experimental cholesterol arteriosclerosis can be elicited in golden hamsters by feeding them a diet of milk and heated egg yolk. In this report it was intended solely to point out that another species of herbivore-rodents responds to cholesterol feeding in addition to the two other species, rabbits and guinea pigs, whose reaction to cholesterol has been described previously.

In 1947, Deuel, Jr.[5] obtained similar results with golden hamsters. Later, Goldman and Pollak[9] and Goldman[8] examined a great number of golden hamsters which had been given cholesterol in capsules. They found that the reaction in their animals could not be classified as atherosclerosis because there was no atheroma formation but only steatosis. Goldman and Pollak concluded that this species "seems ill suited for production of atheromatosis by feeding of cholesterol."

Since my first report on cholesterol feeding to golden hamsters,[1] a few more animals have been added to those on which the first description was based, and the earlier summary statements,[1,2] namely, that golden hamsters react with vascular alterations and with changes in other tissues to the feeding of a diet high in cholesterol, can be confirmed. In view of the just-mentioned negative results of Goldman and Pollak[9] and Goldman,[8] it seemed advisable to publish these observations with some details.

MATERIALS AND METHODS

Eleven golden hamsters were given milk into which dried egg yolk powder had been mixed and yolk cake, a diet described previously.[1,2] The intake of the food varied; some animals liked it more, some less. Their appetite was apparently subject to seasonal changes. The animals were killed after various periods or died spontaneously. The experiments lasted from 53 to 133 days. One animal died naturally, and pieces of it with the greater part of the heart and aorta were eaten by other animals in the cage.

The tissues were prepared in the routine way for paraffin embedding and treated with hematoxylin-eosin, iron hematoxylin, or silver nitrate for von Kóssa's calcium reaction.

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This work was supported by a grant from the Life Insurance Medical Research Fund.
Received for publication June 16, 1950.

RESULTS

In experimental cholesterol arteriosclerosis the major attention is centered on the aorta and the formation of atheroma. Goldman and Pollak[9] were unable to elicit atheromas in their animals and found only "isolated foam cells and groups of two to three foam cells" in the intimal layer of the aorta.

In contrast, in my experiments foam cells formed quite considerable accumulations in the aortic intima (Fig. 1), and this was observed in nine out of ten animals in which the thoracic aorta was examined. In two animals, foam-cell accumulations were also found in the abdominal segment of the aorta. In one animal in which no aortic changes were seen, other vessels showed intimal changes.

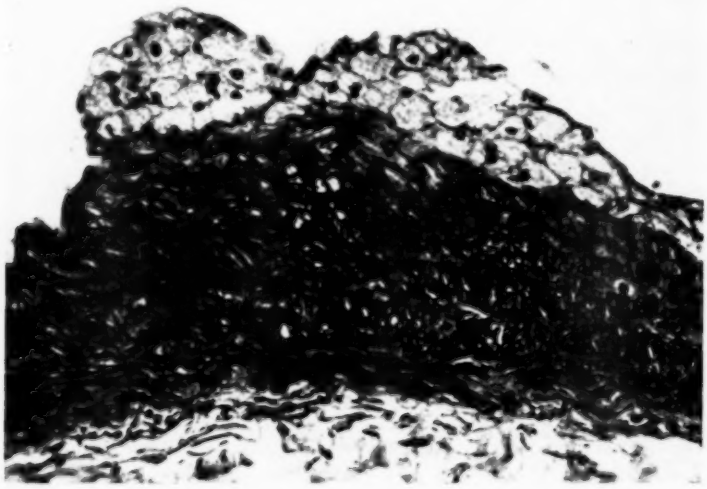

Fig. 1.—Golden hamster. 123 days on a diet of milk and egg yolk. Foam-cell accumulation in aortic arch. Hematoxylin-eosin, × 275.

In some instances, the foam-cell accumulation had decayed into atheromatous masses with or without secondary calcification (Fig. 2, *A* and *B*). Often the height of the atheroma exceeded the thickness of the vessel wall. In one case the necrotic area was covered by a relatively thick fibrotic layer with irregularly shaped cell nuclei.

In one animal, which had been given the diet for eighty days, there was a thrombosis in the pulmonary artery with well-advanced organization of the large thrombus (Fig. 3,*A* and *B*). The latter was attached on one side to a cushion of intimal foam cells, and it seemed reasonable to assume that the thrombosis was a sequel to this intimal change and hence connected with the cholesterol intake.

In cholesterol experiments with rabbits and guinea pigs, the vessels of the tongue and of the heart showed early and extensive changes (see Fig. 10,*A*,*B* and *C*).[2] This was not the case in golden hamsters. Only twice did I encounter

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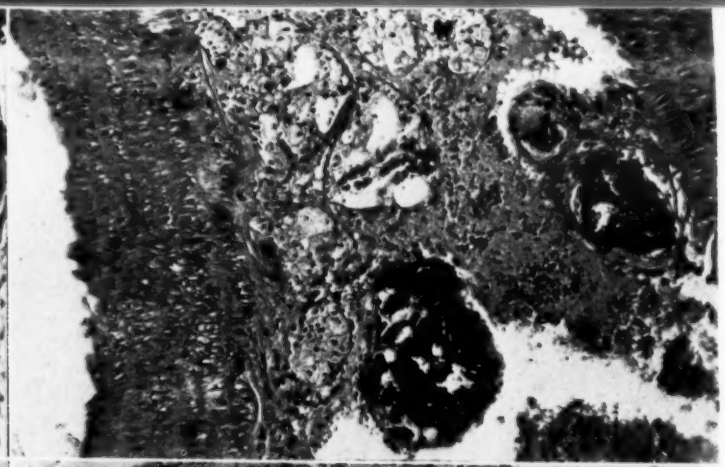

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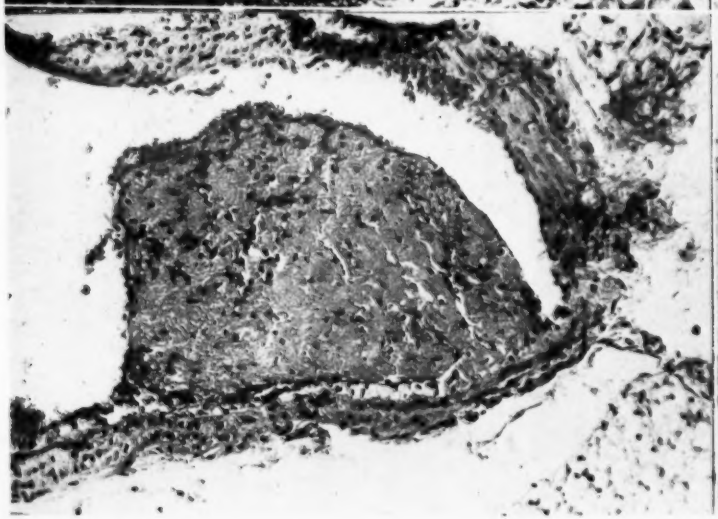

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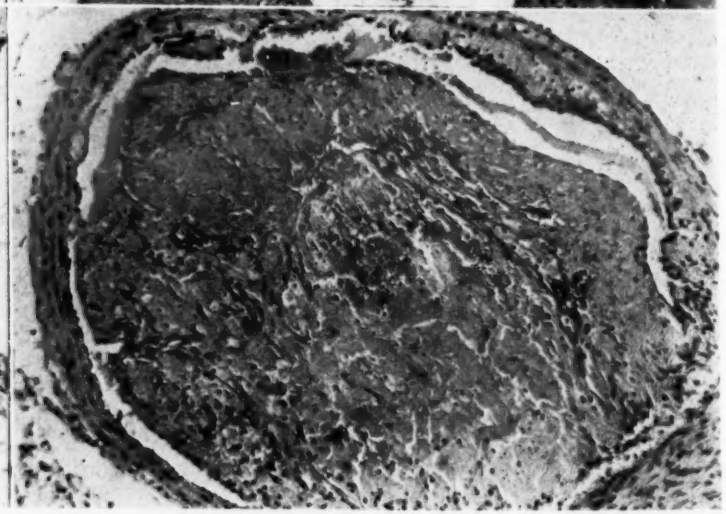

Fig. 2.—Golden hamster, 95 days on diet of milk and egg yolk. *A*, Pulmonary artery with decaying and calcified foam-cell accumulation in the intima. Hematoxylin-eosin, × 125. *B*, Longitudinal section through aortic arch, showing diverticle-like foam-cell accumulations, some of which are calcified. Hematoxylin-eosin, × 105.

Fig. 3.—Golden hamster, 80 days on diet of milk and egg yolk. *A*, Pulmonary artery with hyalinized and organized thrombus, which is attached to an intimal layer of foam cells. Hematoxylin-eosin, × 150. *B*, Cross section of a branch of the pulmonary artery. Thrombus is probably connected with that in preceding figure. Note the reduction of the lumen. Hematoxylin-eosin, × 105.

coronary lesions and in no case an involvement of lingual vessels, in spite of the fact that the skeletal muscle of the tongue and the cardiac muscle frequently showed calcified and hyalinized fibers.

A greatly damaged vessel was seen in a skeletal muscle of one animal. The thickened subendothelial layer formed a ring of atheromatous detritus (Fig. 4). In the choroid plexus of one animal numerous foam cells were seen. They had most likely formed from capillary endothelium as is the case in rabbits.[2]

Besides the atheromatous decay and the formation of foam cells in the vessel wall, there occurred quite frequently a lesion of the media in smaller arteries with calcium deposits (Fig. 5) which recalled the Mönckeberg type of human arteriosclerosis. Whether this alteration was directly connected with the cholesterolemia or caused by an increased intake of vitamin D remains to be seen.

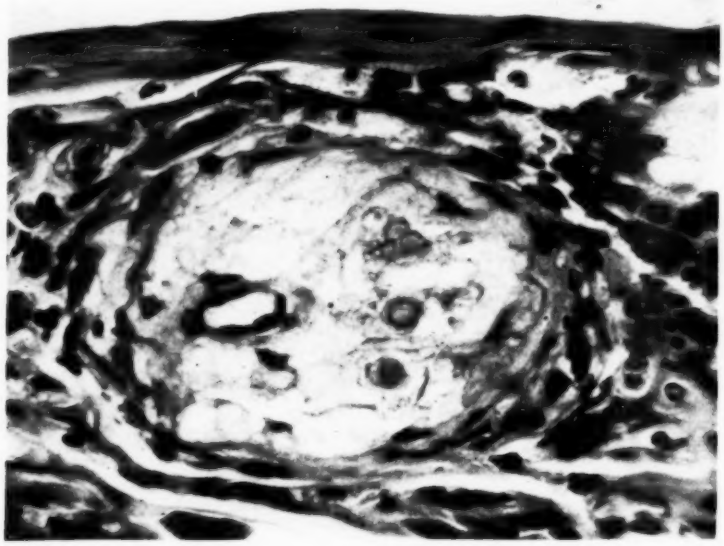

Fig. 4.—Golden hamster, 53 days on a diet of milk and egg yolk. Arteriole from hind leg. The media is thinned, and the space between it and the endothelium is filled with apparently atheromatous material. Hematoxylin-eosin, × 600.

The kidneys frequently presented a reaction in their glomeruli. The endothelium had turned into foam cells (Fig. 6) or the vascular tuft had undergone hyaline degeneration. In one animal the kidneys showed extensive fibrosis surrounding and separating renal tubules (Fig. 7). It is likely that this alteration was caused by vascular disturbances. In another animal there was a typical hemorrhagic infarct.

In a number of cases the spleen showed an excessive number of foam cells, similar to the findings in experiments with rabbits, while in other animals there was only a moderate number of foam cells scattered throughout the organ.

The liver was peculiar in that in all cases its parenchymal cells were morphologically unaltered, although numerous islands of large foam cells had formed and were scattered throughout the organ, giving a speckled appearance to the

Fig. 5. Fig. 6.

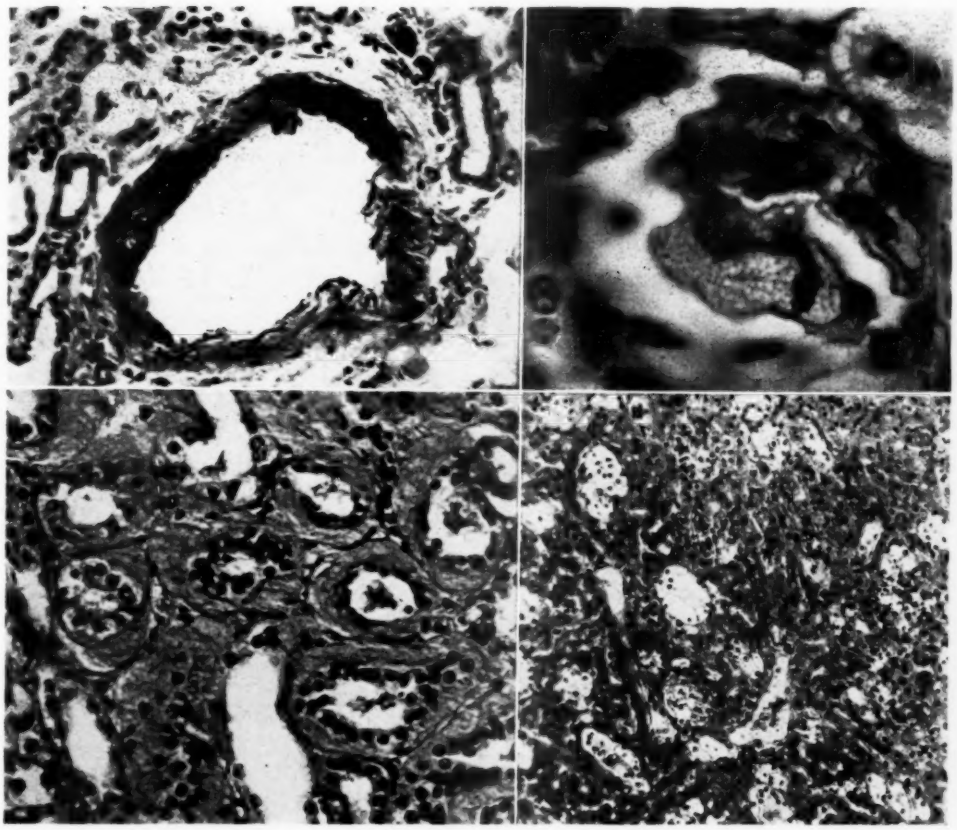

Fig. 7. Fig. 8.

Fig. 5.—Golden hamster, 94 days on a diet of milk and egg yolk. Renal arteriole with partly calcified media. Hematoxylin-eosin, × 220. The lumen has been retouched.

Fig. 6.—Golden hamster, 54 days on a diet of milk and egg yolk. Renal glomerulus. Foam cells, probably forming from capillary endothelium. Hematoxylin-eosin, × 720.

Fig. 7.—Golden hamster, 129 days on a diet of milk and egg yolk. Renal fibrosis. Hematoxylin-eosin, × 240.

Fig. 8.—Golden hamster, 61 days on a diet of milk and egg yolk. Liver with scattered groups of foam cells. Hematoxylin-eosin, × 110.

stained sections (Fig. 8). These foam cells were often fused into multinucleated units. They may probably have originated from Kupffer cells; however, many Kupffer cells showed no indication of foamy transformation.

The suprarenal cortex, which in rabbits and guinea pigs reacts very intensely to cholesterol intake, in our hamsters contained only a moderate number of foam cells scattered throughout the various layers. Their origin may have been the lining cells of the sinuses, although a foam-cell formation from epithelial cells could not be excluded. Goldman[8] made no statement as to the morphological changes in the suprarenal. He only stated that these glands presented a high degree of steatosis.

The lung alveoli in some hamsters were lined by foam cells. It could not be established whether these cells had been formed from endothelium or from alveolar epithelium.

In the occasional case, the lamina propria of the stomach showed greater or lesser amounts of foam cells.

As mentioned before, a response was also observed in tissues other than those of the vessel walls. Skeletal muscle fibers showed a strong reaction. They were frequently hyalinized (waxy degeneration) or calcified. The calcification apparently was secondary to hyalinization and superimposed on the latter. In addition, a granular decay with ensuing proliferation of subsarcolemmal nuclei and immigration of white blood cells was observed. The heart muscle was damaged less extensively than the skeletal muscle. Fewer fibers were calcified after a possible hyalinization preceding the deposition of calcium salts.

In one animal a severe alteration of the thyroid had occurred. The follicles were uneven in size and many of them were filled with a pale staining colloid. Embedded in the colloid of some follicles were foam cells of various sizes. Some of the follicles were almost completely filled with very large foam cells which had fused partly or completely with neighbouring foam cells (Fig. 9,*A*). The colloid also presented clefts, the shape of which suggested that these clefts corresponded to cholesterol crystals dissolved out during the preparation of the tissue (Fig. 9,*B*). Into other empty or colloid-filled follicles protruded epithelial folds. Some of the follicle cells were very pale and were probably in foamy transformation (Fig. 9,*C*).

This thyroid alteration is so far unique. I have not observed it in other experimental animals which had been subjected to an identical or even stronger cholesterol treatment, and, as far as I am aware, no similar change has been reported in the literature.

Other endocrine organs and the gonads showed no morphological changes. Also the uvea of the eye, which in rabbits reacts promptly to cholesterol, appeared completely normal.

According to Goldman,[8] rats and guinea pigs are commonly held to be ill-suited for experimental production of cholesterol atheromatosis. The question whether experimental arteriosclerosis can be elicited in guinea pigs has been discussed before. Duff,[6] after a review of the literature has only "tentatively" accepted the fact that guinea pigs do react to cholesterol intake in spite of previous positive reports. Cook and McCullagh[4] had only a very poor response in guinea pigs. I have found that, although guinea pigs are less susceptible to experimental arteriosclerosis than rabbits, there is no doubt whatever that, in spite of a certain number of negative cases, there are animals which respond with distinct, and sometimes with very strong, vascular changes to the intake of cholesterol. To support this view and to correct Goldman's generalizing statement I have submitted documentary photographs of some fairly typical vascular reactions which were elicited in guinea pigs. These should prove that in guinea pigs experimental cholesterol arteriosclerosis can be produced without great difficulties (Fig. 10, *A*, *B*, and *C*). A more detailed account and additional pictures were given elsewhere.[2]

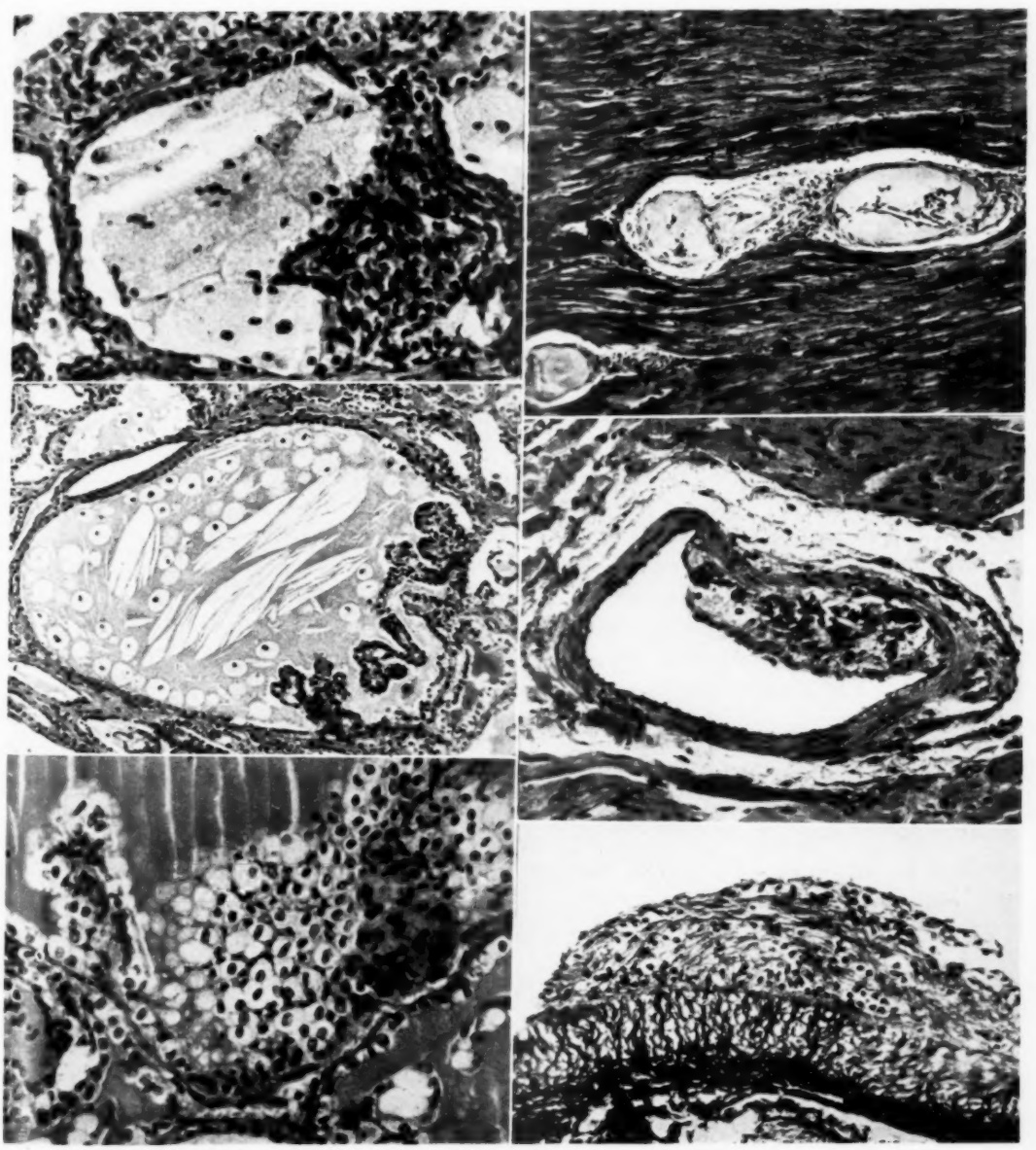

Fig. 9.—Golden hamster, 133 days on a diet of milk and egg yolk. Thyroid gland. Hematoxylin-eosin. *A*, Follicle filled with large foam cells of obscure origin, × 240. *B*, Follicle with numerous foam cells and (cholesterol?) crystals, × 120. *C*, Proliferated follicle epithelium (in foamy transformation?), × 240.

Fig. 10.—Guinea pigs. *A*, 87 days on a diet of milk and egg yolk. Coronary vessel with lipoid cushions. Hematoxylin-eosin, × 60. *B*, 167 days on a diet of milk and egg yolk. Coronary vessel with partly calcified atheroma. Hematoxylin-eosin, × 140. The lumen has been retouched. *C*, 91 days on a diet of milk and egg yolk. Lingual artery with cellular intima cushion. Azan stain, × 160.

DISCUSSION

In previous publications[1,2] it was suggested that the fact that I, in contrast to other workers, had elicited experimental arteriosclerosis in the nervous system and also parenchymal changes in skeletal muscle might be due to the use of heated cholesterol. In heating cholesterol, cholesterol derivatives are formed which may facilitate experimental cholesterol arteriosclerosis. These or similar factors could also account for the different results obtained in golden hamsters by Goldman and by myself.

Moreover, Goldman subjected his animals to daily ether anesthesia. Although this was only light, it remains to be seen whether this procedure did not diminish the cholesterol effect. There are reasons to substantiate this. Alcohol intake is believed by some authorities to mitigate human (Aschoff[3]) and experimental (Eberhard[7]) arteriosclerosis, although its effect in rabbits is being denied (Thiersch[12]). Repeated chloroform anesthesia or benzol inhalations seem to decrease lipoidosis in cholesterol experiments with rabbits.[2] It may be that the numerous ether anesthesias as applied in Goldman's experiments weakened the cholesterol effect, owing to the solubility of cholesterol in ether.

Although the vascular responses in the golden hamsters are less generalized than in the rabbit or guinea pig, it was not difficult to produce typical vascular lesions and parenchymatous reactions. It was even possible in the relatively small number of animals fed milk and heated yolk to produce changes which had not been reported before: the entrance of foam cells into the lumen of thyroid follicles with formation of cholesterol crystals and a thrombosis of a damaged vessel. The absence of this thrombosis in experimental arteriosclerosis has been considered to be an indication that human and experimental arteriosclerosis are not identical (Hueper[10]).

Vagaries of human arteriosclerosis (Moschcowitz[11]) and the unruliness of experimental arteriosclerosis (Altschul[2]) are a well-recognized feature. Some irregularity or difficulty in eliciting vascular reactions in golden hamsters should not be taken as a proof that this species is ill-suited for experimental arteriosclerosis.

SUMMARY

The feeding of a diet of milk and egg yolk to golden hamsters produces vascular and parenchymal reactions similar to those observed in rabbits under similar or identical conditions. In one animal the thyroid showed changes which had not yet been reported. In another animal extensive thrombosis was present, which probably was caused by the intimal changes.

The feeding of the same diet to guinea pigs produces cholesterol arteriosclerosis in a large proportion of these animals, a fact not generally recognized by other authors.

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ELECTROKYMOGRAPHIC STUDIES OF ABNORMAL LEFT VENTRICULAR PULSATIONS

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STUDIES of abnormal left ventricular pulsations have long been of interest. Such pulsations after myocardial infarction were investigated by means of the roentgenkymograph by Stumpf and associates,[1] Gubner and associates,[2] Sussman and co-workers,[3,4] and Roesler.[5] The development of the electrokymograph[6-15] has permitted more detailed study both of normal and abnormal left ventricular waves. With this latter technique more complete and accurate investigations are possible for several reasons: (1) The time of each portion of the left ventricular phase is obtained by simultaneous recording of a carotid artery pulse tracing. (2) As many cardiac cycles as desired can be recorded successively. (3) Selection of the points most likely to show abnormalities on the recorded curves is made possible by the simultaneously required fluoroscopic selection of these regions. (4) Simultaneous electrocardiographic studies are possible if desired.

Some work has already been published on the types of abnormal curves that may be obtained.[12-17,35] In the main, these have been in accord with the findings noted on roentgenkymography. However, the studies of left ventricular pulsations after myocardial infarction with the electrokymograph have been limited to relatively few cases, the twenty cases reported by Luisada and Fleischner[16] constituting by far the largest portion of such cases. We therefore undertook a study of a larger series of such patients with the electrokymograph.

TECHNIQUE

We have studied the left ventricular electrokymographic pattern in thirty-one cases of anterior wall myocardial infarction, twenty-eight cases of posterior wall infarction, and eleven cases of combined anterior and posterior wall infarction. In all seventy cases the diagnosis was supported by the history, physical examination, laboratory work, clinical course, and the electrocardiogram. In most cases at least twelve leads, including the three standard leads, the three unipolar

From the Cardiac Section of the Medical Service, Bronx Veterans Hospital.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the results of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Received for publication April 4, 1950.

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limb leads, and six unipolar chest leads with a Wilson terminus, were recorded. The precordial region was often further explored electrocardiographically with unipolar leads at positions other than the standard unipolar precordial positions. In addition, studies were made of five patients whose history, physical examination, laboratory work, and clinical course strongly suggested the diagnosis of myocardial infarction, but in whom the electrocardiographic pattern of myocardial infarction was obscured by the presence of left bundle branch block. The electrokymographic studies in these seventy-five patients were all made at least six six weeks after the acute attack heralding myocardial infarction, and little can therefore be said about possible changing patterns immediately after a myocardial infarction. Abnormal left ventricular pulsations were recorded in ten other patients with enlarged hearts due to various causes, but in whom there was little to suggest myocardial infarction either in the history, physical examination, or electrocardiographic studies. In all, therefore, eighty-five cases were studied.

We have employed the technique of simultaneous electrokymography in order to make possible a complete, yet fairly rapid, method for detailed studies of left ventricular pulsations. Two electrokymographs with two photoelectric pickup units were therefore employed simultaneously, these units being placed at two different points along the left ventricular border. In this manner at least six points on the left ventricle were studied in each of three positions, the posteroanterior, the right anterior oblique, and the left anterior oblique, two points being recorded simultaneously. The tracings were recorded on a three-channel direct-writing Technicon.* Two channels were employed to record the electrokymograms. The carotid artery pulse wave or the electrocardiogram was recorded on the third channel (usually the former) because the various phases of the left ventricular electrokymogram can be more adequately timed with a mechanical curve (the carotid artery pulse wave) rather than with an electrical curve (the electrocardiogram). The carotid pulse pickup unit consists of a microphone with transmission set at a relatively low frequency. It is placed directly over the pulsating vessel so that only pressure tracings are obtained. There is a time lag of 0.03 second on the carotid artery pulse wave compared to the ventricular electrokymogram. This 0.03 second represents the time necessary for the pulse wave to travel from the aortic valve to the carotid artery in the neck and through the soft tissues of the neck to be picked up by the electrical carotid artery pulse wave recorded. Therefore, when comparing corresponding points on the ventricular electrokymogram and the carotid artery pulse wave, one must take this lag into account.

The electrokymographic curves were all taken in the posteroanterior and right and left anterior oblique positions with the patient sitting on a low stool. The fluoroscopy was done by one of us (J.B.S.) in all cases. A fully rectified fluoroscope was employed with the operating factors set at 4 to 5 Ma., and at 70 to 74 kv. The curves were recorded at a paper speed of 25 mm. per second. The distance between two heavy lines represents 0.2 second, and that between two light lines represents 0.04 second as on the ordinary electrocardiographic

*The Technicon Corporation, 215 East 149th Street, New York, N. Y.

machine. After the study was completed, the data were analyzed with the following points in mind: (1) incidence of abnormal, expecially paradoxical. pulsations noted fluoroscopically; (2) incidence of abnormal, especially paradoxical, pulsations noted on the electrokymograph; (3) types of abnormal pulsations noted on the electrokymograph; (4) correlation of the incidence of abnormal pulsations on fluoroscopy and electrokymography; and (5) correlation of the electrocardiographic site of infarction and the site of infarction noted on the electrokymogram.

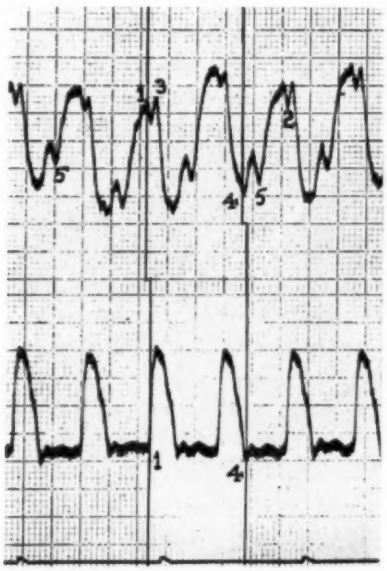


Fig. 1.—The upper curve is an electrokymogram of a normal left ventricle in the posteroanterior position. The lower curve is a carotid artery pulse curve. Point *1* represents onset of the isometric contraction phase; point *2* is the end of that phase and the start of ejection. Point *4* represents closure of the aortic valve and onset of the isometric relaxation phase; point *5* represents the end of that phase and the opening of the auriculoventricular valve. Note the 0.03 second time lag on the electrokymograms. This lag factor is present in all subsequent figures. See text for further details.

RESULTS

Familiarity with the normal left ventricular electrokymographic curve is of course essential for an understanding of the abnormal curves. Fig. 1 illustrates the curves obtained in a normal individual. The outward expansion of the left ventricular curve between points *2* and *3* is due to torsional and rotational movements of the heart. Note that the lowermost part of the left ventricular curve is at point *4* and that point *5* is at the same level or higher than point *4*. Rarely, point *5* may be lower than point *4* and simulate (in a normal patient) an abnormal early diastolic collapse as represented by a downstroke of the left ventricular curve after point *4*. We have observed this latter phenomenon along the posterior wall of the left ventricle in the left anterior oblique position, but never in the posterioanterior position. Luisada and Fleischner[16] and Boone and associates[11] have made similar observations in normals.

Table I shows our results in thirty-one cases of anterior wall myocardial infarction. The third column from the left gives information as to the presence or absence of a paradoxical pulsation on fluoroscopy. Normally, on fluoroscopy the left ventricular contour moves inward in systole and outward in diastole. On the electrokymogram normally the inward systolic movement registers as a downstroke while the outward diastolic movement registers as an upstroke. Abnormal left ventricular pulsations are mainly of two types. An outward movement on fluoroscopy or an upward movement on electrokymography in systole constitutes systolic expansion. Inward movement on fluoroscopy or downward movement on electrokymography in diastole constitutes diastolic collapse. Since systolic expansion and diastolic collapse represent movements of the left ventricular contour in a direction opposite to that normally present, such

TABLE I. GROUP A: CASES OF MYOCARDIAL INFARCTION WITH DIAGNOSTIC CLINICAL AND ELECTROCARDIOGRAM FINDINGS

	NAME	ANTERIOR WALL INFARCTS: DIAGNOSIS	PARADOXICAL PULSATION FLUOROSCOPICALLY	ELECTROKYMOGRAM		CORRELATION OF ECG AND EKY
				SYSTOLIC	DIASTOLIC	
1	S. S.	ASHD	Mid and lower left ventricle	Early expansion	Collapse	Yes
2	B. B.	ASHD	Mid left ventricle	Early expansion	Collapse	Yes
3	M. B.	ASHD	Lower ¾ left ventricle	Early expansion	Collapse	Yes
4	M. G.	ASHD	Entire left ventricle	Late expansion upper left ventricle; Early expansion lower left ventricle	Collapse Collapse	Yes
5	S. P.	ASHD	None		Collapse	Yes
6	P. L.	ASHD	None		Collapse	Yes
7	P. A.	ASHD	None	None		
8	J. G.	ASHD	Paradoxical	Early expansion	Collaps	Yes
9	S. A.	ASHD	Paradoxical	Early expansion	Collapse	Yes
10	G. B.	ASHD	Paradoxical	Early expansion	Collapse	Yes
11	I. M.	ASHD	Paradoxical entire left ventricle	Early expansion	Collapse	Yes
12	M. R.	ASHD	None	Early expansion	Collapse	Yes
13	M. S.	ASHD	None	None		
14	E. C.	ASHD	None	None		
15	M. B.	ASHD	Paradoxical	Early expansion	Collapse	Yes
16	H. N.	Hyp. ASHD	Paradoxical	Early expansion	Collapse	Yes
17	A. F.	ASHD	Paradoxical	Early expansion	Collapse	Yes
18	R. A.	ASHD	Paradoxical	Early expansion	Collapse	Yes
19	W. A.	ASHD	Paradoxical		Collapse	Yes
20	W. C.	Hyp. ASHD	Paradoxical		Collapse	Yes
21	B. M.	ASHD	Paradoxical	Early expansion	Collapse	Yes
22	F. L.	ASHD	Paradoxical	Early expansion	Collapse	Yes
23	J. S.	ASHD	Paradoxical	Early expansion	Collapse	Yes
24	N. H.	ASHD	None	None		
25	J. S.	ASHD	None	None		
26	H. N.	ASHD	Paradoxical	Late expansion	Collapse	Yes
27	K. W.	ASHD	None	None		
28	S. R.	Hyp. ASHD	None	None		
29	M. M.	ASHD	None	None		
30	A. B.	Hyp. ASHD	None	None		
31	W. G.	ASHD	Paradoxical	Early expansion	Collapse	Yes

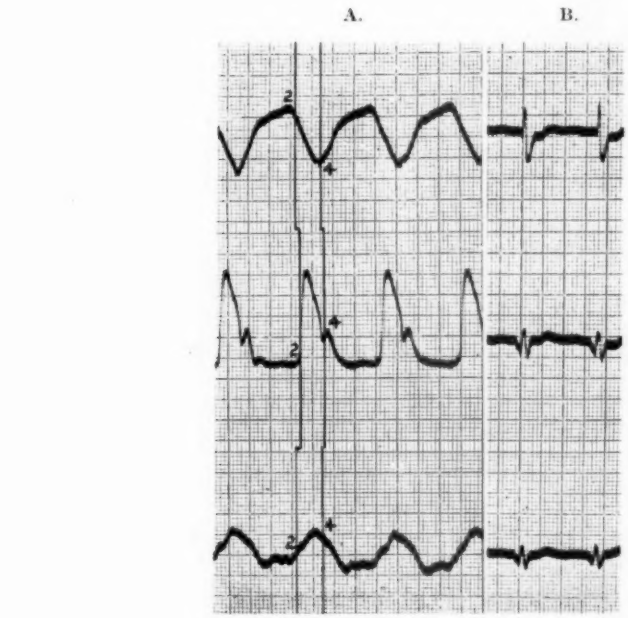
ASHD = Arteriosclerotic heart disease.
Hyp. ASHD = Hypertensive and arteriosclerotic heart disease.
EKY = Electrokymogram.
ECG = Electrocardiogram.

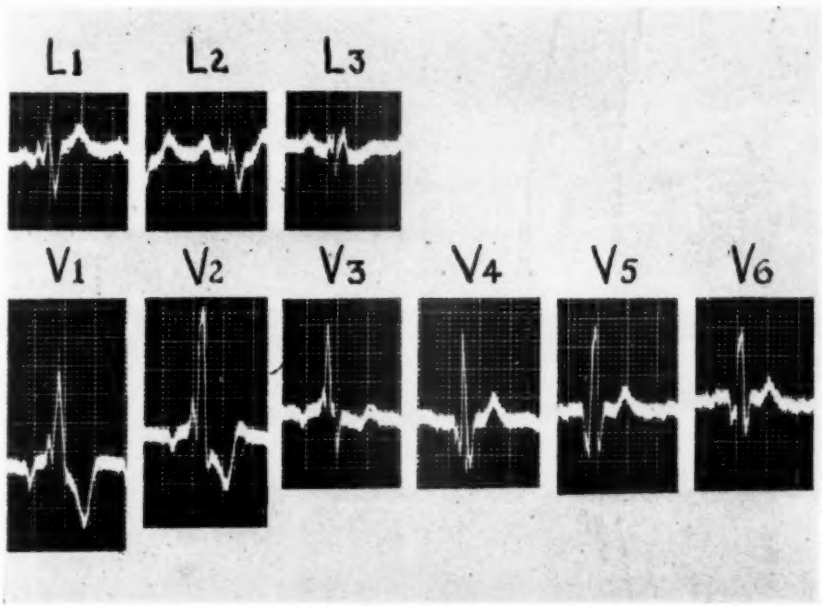
movements are called paradoxical. In the column of Table I labeled Paradoxical Pulsation Fluoroscopically, we have listed the incidence of paradoxical pulsations noted fluoroscopically. In the next column is listed the incidence and type of paradoxical pulsation noted with the electrokymograph. In the column to the right we have recorded the correlation of the electrokymogram and the electrocardiogram. Since this group of thirty-one patients all had anterior wall infarcts, we feel that correlation is present if paradoxical pulsations of the left ventricle are noted in either the right anterior oblique position or the posteroanterior position. It is interesting to note that nineteen of the thirty-one cases showed paradoxical pulsation on fluoroscopy in the posteroanterior position, while twelve did not. All nineteen showed paradoxical pulsation on the electrokymogram, but, in addition, three of the twelve who did not show paradoxical pulsations on fluoroscopy showed paradoxical pulsations on the electrokymogram. Correlation of the electrocardiogram and the electrokymogram was present in all cases. That is, paradoxical pulsation of the left ventricle when present (in those cases where the electrocardiogram showed anterior wall infarction) was noted on the anterior or lateral wall of the ventricle in the right anterior oblique or posteroanterior positions, respectively. One further point deserves comment. In most cases where paradoxical pulsation was noted, it was of the early systolic expansion and early diastolic collapse type. Late systolic expansion was noted only in Cases 4 and 26, M. G., and H. N., respectively.

Figs. 2 to 4 illustrate some of our tracings.

Fig. 2,*A* shows the tracings of patient S. A. recorded in the posteroanterior position. The middle curve is the carotid artery pulse wave. The uppermost curve is that of the relatively normal left ventricle with a downstroke at point *2* (onset of ventricular ejection) and an upstroke after point *4* (closure of the aortic valve). In contrast, the abnormal lower ventricular curve shows an early systolic expansion at point *2* and early diastolic collapse after point *4*. There is thus expansion in systole and collapse in diastole. The pulsations are opposite in direction to the normal and are thus paradoxical in character. Fig. 2,*B* shows Leads V_4, V_5, and V_6 of the electrocardiogram. Fig. 2,*C* shows the full electrocardiogram.

Fig. 3 shows the tracing of patient S. S. Fig. 3,*A* is a tracing taken in the left anterior oblique position of the upper and lower left ventricle, respectively, with cessation of respiration at the end of a normal expiration; it demonstrates relatively normal tracings. Fig. 3,*B* shows a tracing taken over the same two points at the end of deep inspiration. Note the markedly abnormal diastolic collapse in the tracings at the end of deep inspiration. This is a phenomenon we have repeatedly observed. A normal curve may be obtained at the end of a normal expiration, while a markedly abnormal curve showing systolic expansion or diastolic collapse is noted when the tracings are recorded at the end of deep inspiration. Note also that when early diastolic collapse occurs, there is rapid filling or expansion late in diastole instead of the normally occurring, rapid, early diastolic expansion. In this figure note also that there is abnormal early systolic expansion on both ventricular curves. In Fig. 3,*C* the uppermost curve is the carotid pulse tracing, while the lower two curves show early diastolic collapse in





C.

Fig. 2.—*A* illustrates the tracings of patient S.A., Table I, recorded in the posteroanterior position. The upper curve is that of the relatively normal left ventricle, the mid-curve is the carotid pulse wave, and the lower curve is that of the abnormal lower ventricular border. Systolic and diastolic paradoxical pulsations are present on the lower curve.

B shows V_4, V_5, and V_6 at one-half N standardization.

C shows the full electrocardiogram demonstrating right bundle branch block with deep Q waves in the precordial leads from the left side, diagnostic of anterior wall myocardial infarction.

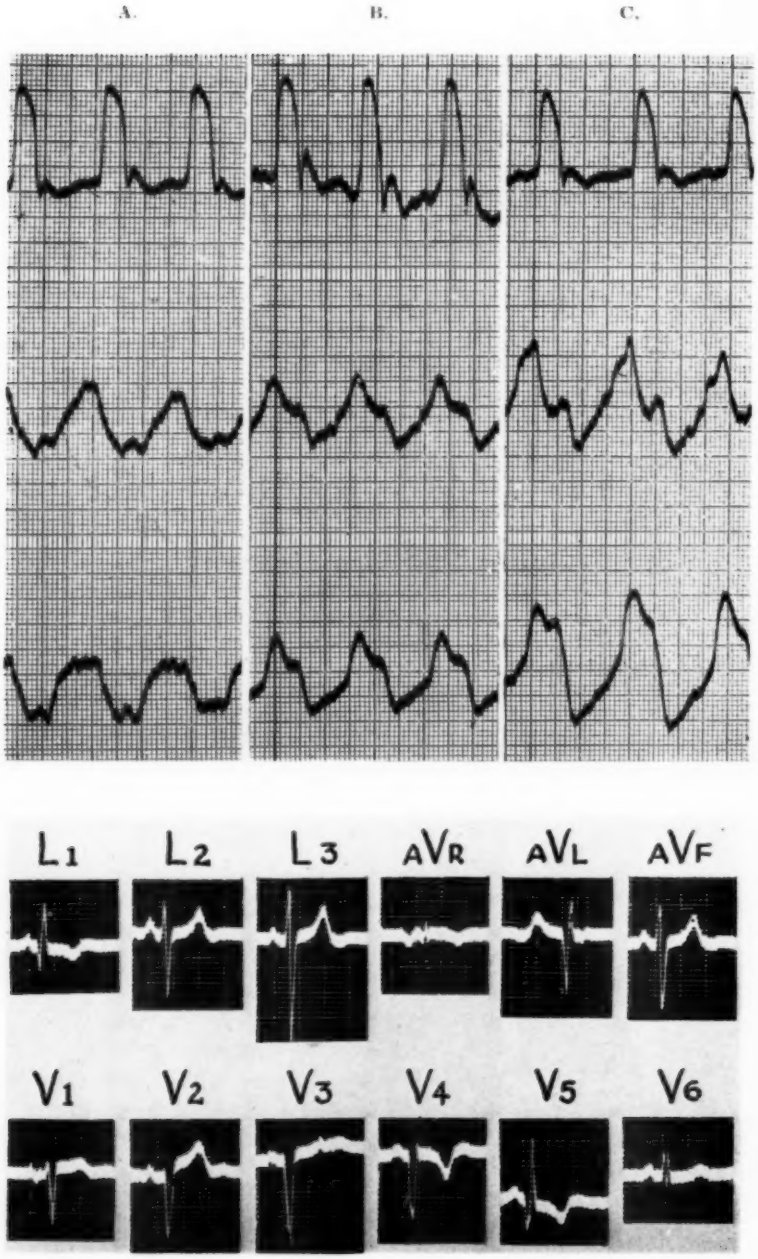


Fig. 3.—*A*, The carotid curve and electrokymograms of the upper and lower left ventricle in the left oblique position of patient S.S., Table I, at the end of normal expiration.

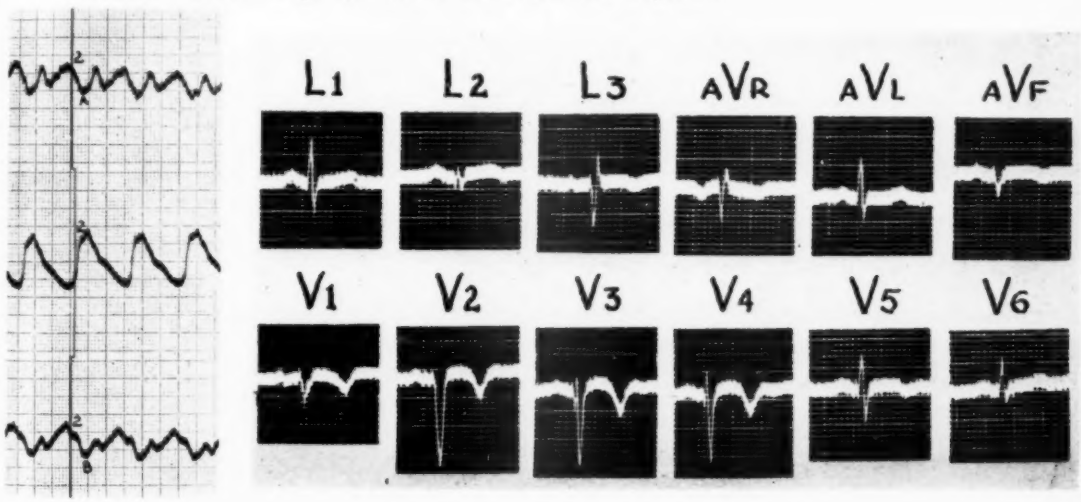
B, Tracings of the same points at the end of a deep inspiration are shown. Note the markedly abnormal curves in Fig. 4,*B* only. See text for further discussion.

C illustrates abnormal curves in the posteroanterior position.

D shows the electrocardiographic pattern of anterior wall infarction.

tracings from the midportion of the left ventricle in the posteroanterior position. Fig. 3,*D* illustrates the electrocardiogram.

Fig. 4,*A* illustrates the curves obtained in patient H. N., No. 26. The uppermost curve is that of the upper left ventricle, the midcurve is that of the carotid artery pulse, and the lowermost is the electrokymogram of the lower left ventricle in the posteroanterior position. Note that systolic ejection starts at point 2 on the carotid curves and electrokymograms. In the upper curve there is an abortive midsystolic expansion noted along the descent of the curve at point *A*, while in the lower curve there is a definite mid-late systolic expansion noted at point *B*. In other words, the ventricular muscle starts to contract at the beginning of systole and the electrokymographic curve moves downward, but in mid to late systole the intraventricular pressure causes an outward expansion of a damaged ventricular musculature at points *A* and *B*. Whether such systolic expansion represents less ventricular wall damage than early systolic expansion remains conjectural. Early diastolic collapse is present on both ventricular curves. Fig. 4,*B* shows the electrocardiogram.



A. B.

Fig. 4.—*A* portrays the tracings of patient H.N., Table I. The mid-curve is the carotid pulse tracing. The upper and lower curves show the electrokymograms of the upper and lower left ventricle in the posteroanterior position. Systolic expansion and diastolic collapse are shown on both curves. See text for further details.

***B* shows the electrocardiographic pattern of anteroseptal infarction. A small R wave is present in Leads III and aV$_F$.**

Table II shows our results in twenty-eight cases of posterior wall myocardial infarction. In eleven cases paradoxical pulsation was noted on fluoroscopy in the posteroanterior position only along the lateral border of the heart. In six cases paradoxical pulsations were noted both in the posteroanterior and left anterior oblique positions on fluoroscopy. But in no case was paradoxical pulsation of the posterior wall of the left ventricle in the left anterior oblique position noted without paradoxical pulsations also being recorded in the posteroanterior position. Therefore, in seventeen of the twenty-eight cases paradoxical

TABLE II. GROUP B: CASES OF MYOCARDIAL INFARCTION WITH DIAGNOSTIC CLINICAL AND ELECTROCARDIOGRAM FINDINGS

	NAME	POSTERIOR WALL INFARCTION: DIAGNOSIS	PARADOXICAL PULSATION FLUOROSCOPICALLY	ELECTROKYMOGRAM		CORRELATION OF ECG AND EKY
				SYSTOLIC	DIASTOLIC	
1	G. F.	ASHD	None	None		
2	S. S.	ASHD	None	Early expansion		Yes
3	A. R.	ASHD	Paradoxical, PA only	Mid-systolic expansion, PA only	Collapse, PA only	None
4	J. F.	ASHD	None	None		
5	A. S.	ASHD	None	None		
6	A. M.	ASHD	Paradoxical, PA only		Collapse, PA only	None
7	W. N. Q.	ASHD	Paradoxical, PA only	Early expansion, PA only	Collapse, PA only	None
8	M. C.	ASHD	None	None		
9	E. B.	ASHD	Paradoxical, PA and LAO	Mid-systolic expansion	Collapse	Yes
10	A. P.	ASHD (Post.Lat.Inf.)	Paradoxical, PA only	Early systolic		None
11	J. F.	ASHD	None	Early systolic		None
12	T. O'B.	ASHD	None	None		
13	F. K.	ASHD	Paradoxical, PA only		Collapse	None
14	G. Y.	ASHD (Post.Lat.Inf.)	Paradoxical, PA only		Collapse	None
15	F. M.	ASHD (Post.Lat.Inf.)	Paradoxical, PA only	Early expansion	Collapse	None
16	P. B.	ASHD	None	Early systolic	Collapse	None
17	S. L.	ASHD (Post.Lat.Inf.)	None		Collapse, PA and LAO	Yes
18	V. C.	ASHD	Paradoxical, PA and LAO		Collapse, PA and LAO	Yes
19	H. S.	ASHD	Paradoxical, PA only		Collapse, PA and LAO	Yes
20	M. C.	ASHD	Paradoxical, PA and LAO	Early systolic, PA and LAO	Collapse, PA and LAO	Yes
21	J. G.	ASHD	Paradoxical, PA only	Early systolic		None
22	J. Q.	ASHD	None	None		None
23	J. S.	ASHD (Post.Lat.Inf.)	None	None		
24	F. C.	ASHD	Paradoxical, PA and LAO	Early systolic, PA only	Collapse, PA and LAO	Yes
25	C. C.	Hyp. ASHD	Paradoxical, PA only	Mid-systolic expansion, PA only		None
26	S. DuB.	ASHD (Post.Lat.Inf.)	Paradoxical, PA only		Collapse, PA only	None
27	E. N.	Hyp. ASHD	Paradoxical, PA and LAO		Collapse, PA and LAO	Yes
28	H. B.	Hyp. ASHD	Paradoxical, PA and LAO		Early and late collapse, PA and LAO	Yes

ASHD = Arteriosclerotic heart disease.
Hyp. ASHD = Hypertensive and arteriosclerotic heart disease.
EKY = Electrokymogram.
ECG = Electrocardiogram.
Post. Lat. Inf. = Posterolateral myocardial infarction.
PA = Posteroanterior position.
LAO = Left anterior oblique position.

pulsations were noted on fluoroscopy. Every one of these seventeen cases had paradoxical pulsations on the electrokymogram. Of the eleven cases showing no paradoxical pulsation on fluoroscopy, seven showed no paradoxical pulsations on the electrokymogram, while the remaining four demonstrated paradoxical pulsations in either the posteroanterior or left anterior oblique positions. We have noted that paradoxical pulsations (in these abnormals) in the oblique electrokymograms were always accompanied by paradoxical pulsations in the posteroanterior electrokymograms. Indeed, several patients with posterior wall infarction on the electrocardiogram had paradoxical pulsations in the electrokymograms taken in the posteroanterior position but not those taken in the left oblique position. We, therefore, note lack of correlation between the electrocardiographic and electrokymographic pictures in twelve of the twenty-eight cases—twelve cases where the electrocardiogram was diagnostic of a posterior wall infarct, yet the electrokymogram showed paradoxical pulsations only in the posteroanterior position. In nine patients with posterior wall myocardial infarction correlation between the electrocardiogram and electrokymogram was noted in that all nine demonstrated paradoxical pulsations along the posterior wall of the left ventricle in the left oblique position. The presence of correlation denotes that electrokymographic paradoxical pulsations were noted (when present) in both the posteroanterior and left oblique positions, since the latter was not observed without the former.

Fig. 5 illustrates our results in this latter group of cases. In Fig. 5 the tracings of patient E. B. are pictured. Fig. 5,*A* shows the carotid artery pulse curve above and electrokymograms of the upper and lower left ventricle below, taken in the posteroanterior position. Early and mid-systolic expansion is noted in both curves, while the middle curve in addition demonstrates a marked diastolic collapse. Fig. 5,*B* shows the same curves taken in the right anterior oblique position and illustrates early and mid-systolic expansion with a systolic downstroke later in systole in both curves, together with early diastolic collapse in the middle curve from the upper left ventricular border. Fig. 5,*C* shows the electrocardiogram.

Table III demonstrates the results in eleven cases of combined anterior and posterior wall infarction. Cases 1, 3, and 4 have paradoxical pulsations in the posteroanterior and left oblique positions on both fluoroscopy and electrokymography. Since the electrocardiogram shows combined anterior and posterior wall infarction, there is complete correlation between the electrokymogram and electrocardiogram in these three cases. In the remaining eight cases paradoxical pulsation was noted only in the posteroanterior position on fluoroscopy. However, the electrokymogram showed paradoxical pulsation in the left oblique position in two of these eight cases, in addition to paradoxical pulsation in the posteroanterior position in all eight. Therefore, these two cases show correlation between the electrokymogram and electrocardiogram in both positions, while the other six show correlation only in the posteroanterior position. In Fig. 6,*A* the tracings of W. O'C. are illustrated. The electrokymogram of the upper and mid left ventricle and the carotid curve are shown from above down in the posteroanterior position. The upper curve contains a mid-systolic expansion

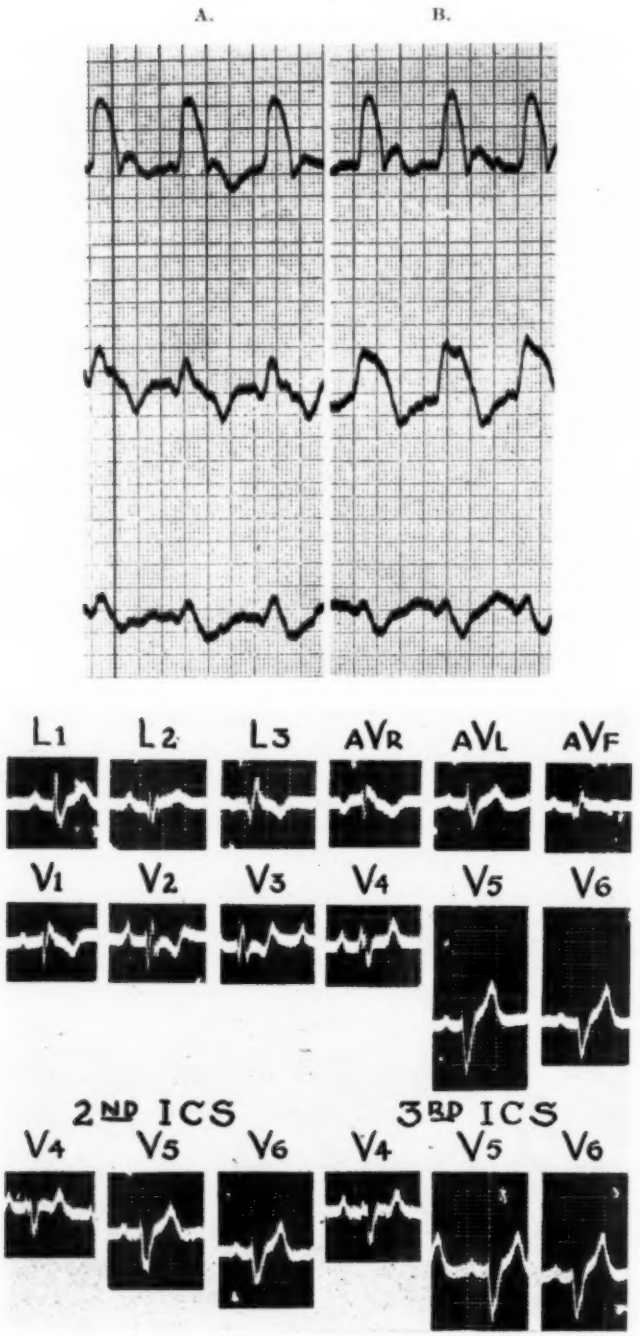
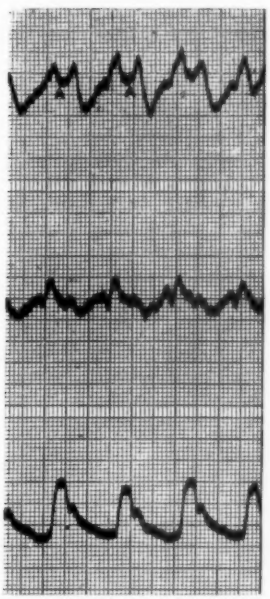


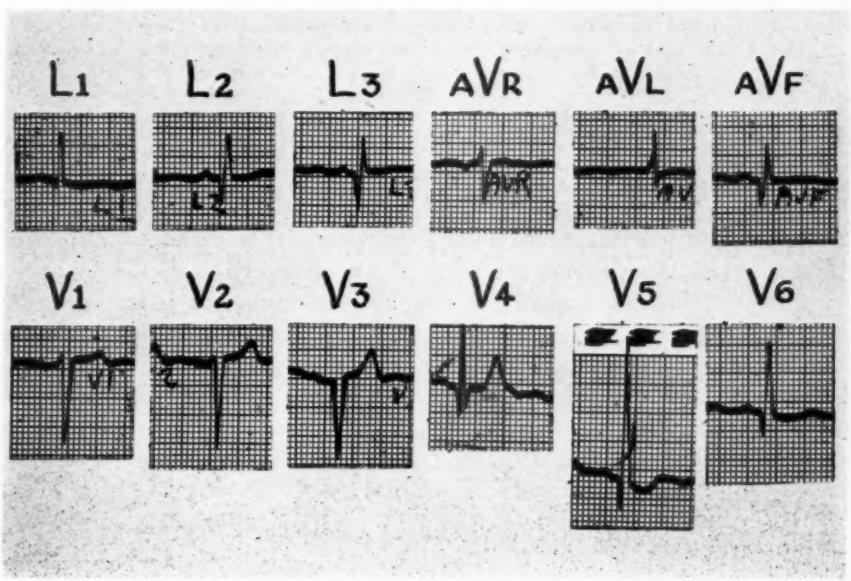
Fig. 5.—*A* shows the curves of patient E.B., Table II, taken in the posteroanterior position.

B shows curves taken with the patient in the right oblique position. Systolic and diastolic abnorma patterns are evident. These are fully discussed in the text.

C shows the electrocardiographic findings in posterior wall myocardial infarction.

A.





B.

Fig. 6.—*A* illustrates the tracings of W. O'C., Table III. The electrokymogram of the upper and mid left ventricle and the carotid curve are shown from above down in the posteroanterior position. The abnormal features are discussed in the text.

B shows the electrocardiogram with features of anterior and posterior wall myocardial infarction.

component starting at point *A*, while both curves demonstrate early diastolic collapse with resulting rapid filling in late diastole (instead of early diastolic filling as is normal). Fig. 6,*B* is the electrocardiogram.

TABLE III. GROUP C: CASES OF MYOCARDIAL INFARCTION WITH DIAGNOSTIC CLINICAL AND ELECTROCARDIOGRAM FINDINGS

	NAME	ANTERIOR AND POSTERIOR INFARCTION: DIAGNOSIS	PARADOXICAL PULSATION FLUOROSCOPICALLY	ELECTROKYMOGRAM		CORRELATION OF ECG AND EKY
				SYSTOLIC	DIASTOLIC	
1	N. L.	ASHD	Upper half left ventricle		Collapse in PA and LAO	Yes, both positions
2	W. O'C.	ASHD	Lower half left ventricle, PA only	Mid-systolic	Collapse, PA	Yes, PA only
3	J. D.	Hyp. ASHD	Lower half left ventricle		Collapse	Yes, both positions
4	N. McA.	ASHD	Paradoxical	Early expansion	Collapse	Yes, both positions
5	S. F.	ASHD	Paradoxical, PA only	Early expansion	Collapse	Yes, PA only
6	C. S.	ASHD	Paradoxical, PA only	Early expansion	Collapse	Yes, both positions
7	M. M.	ASHD	Paradoxical, PA only	Early expansion	Collapse	Yes, PA only
8	P. C.	Hyp. ASHD	Paradoxical, PA only	Early expansion	Collapse	Yes, PA only
9	S. S.	Hyp. ASHD	Paradoxical, PA only		Collapse, PA and LAO	Yes, both positions
10	S. R.	ASHD	Paradoxical, PA only	Early expansion, PA only	Collapse, PA only	Yes, PA only
11	W. M.	ASHD	Paradoxical, PA only	Early expansion, PA only	Collapse, PA only	Yes, PA only

ASHD = Arteriosclerotic heart disease.
Hyp. ASHD = Hypertensive arteriosclerotic heart disease.
EKY = Electrokymogram.
ECG = Electrocardiogram.
PA = Posteroanterior position.
LAO = Left anterior oblique position.

In Table IV our results in ten patients with marked cardiac enlargement are listed. Abnormal left ventricular pulsations with paradoxical pulsations were noted in all ten despite the lack of historical, clinical, laboratory, and electrocardiographic evidence for myocardial infarction. It is interesting that aortic insufficiency was present in all cases of the first subdivision of Group D and was the predominant cause for the cardiac enlargement in all cases. All five patients of this first subdivision were in congestive heart failure when the tracings were recorded. Paradoxical pulsation was noted in all five on fluoroscopy. Early and late systolic expansion and early diastolic collapse were noted in the electrokymographic curves in these five cases.

In the second subdivision of Group D, paradoxical pulsations were again noted in all cases despite the lack of any evidence suggesting myocardial infarction. In Fig. 7,*A* the carotid pulse and electrokymograms of the upper and lower left ventricles are shown from above down in patient F. Y., taken in the right oblique position. The middle curve demonstrates marked diastolic collapse, while the lower curve demonstrates early systolic expansion at point *A* and mid-diastolic collapse at point *B*. The electrocardiogram is noted in Fig. 7,*B*.

TABLE IV. GROUP D: CASES SHOWING PARADOXICAL PULSATION OF THE LEFT VENTRICLE WITHOUT CONFIRMATORY CLINICAL OR ELECTROCARDIOGRAM FINDINGS FOR MYOCARDIAL INFARCTION

1. With Aortic Insufficiency Causing Cardiac Enlargement

	NAME AND AGE	DIAGNOSIS	PARADOXICAL PULSATIONS FLUOROSCOPICALLY	ELECTROKYMOGRAM	
				SYSTOLIC	DIASTOLIC
1	H. M. 44	Rh. H. D.	Paradoxical, PA mid left ventricle	Early expansion	Collapse
2	A. B. 30	Rh. H. D.	Paradoxical, PA lower left ventricle	Early expansion	
3	H. R. 54	Rh. H. D.	Paradoxical		Collapse
4	C. M. 46	Syphilitic H. D.	Paradoxical		Collapse
5	C. L. 60	Syphilitic H. D.	Paradoxical		Collapse

2. Other Causes of Enlarged Heart

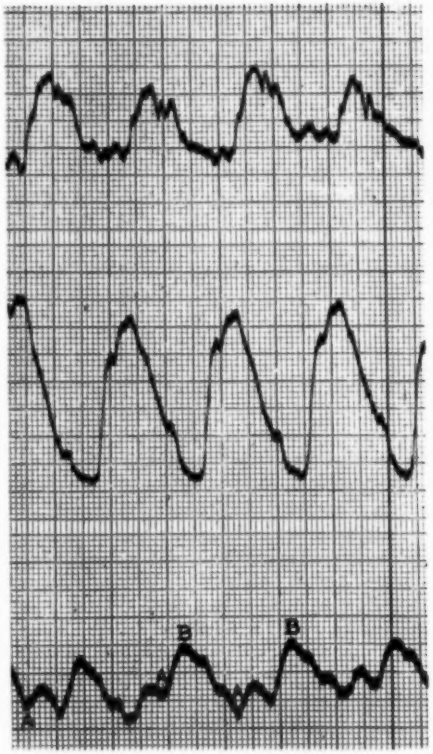
6	A. T.	Hyp. ASHD	Paradoxical, PA mid left ventricle		Collapse
7	A. S.	ASHD	Paradoxical apex left ventricle	Late expansion	Collapse
8	M. N.	Hyp. ASHD	Paradoxical, PA lower left ventricle	Early expansion	Collapse
9	J. G.	Hyp. ASHD	Paradoxical	Early expansion	Collapse
10	F. Y.	Hyp. ASHD	Paradoxical	Early expansion	Mid-diastolic collapse and early diastolic collapse

ASHD = Arteriosclerotic heart disease.
Hyp. ASHD = Hypertensive arteriosclerotic heart disease.
EKY = Electrokymogram.
ECG = Electrocardiogram.
Rh. H. D. = Rheumatic heart disease.
PA = Posteroanterior position.

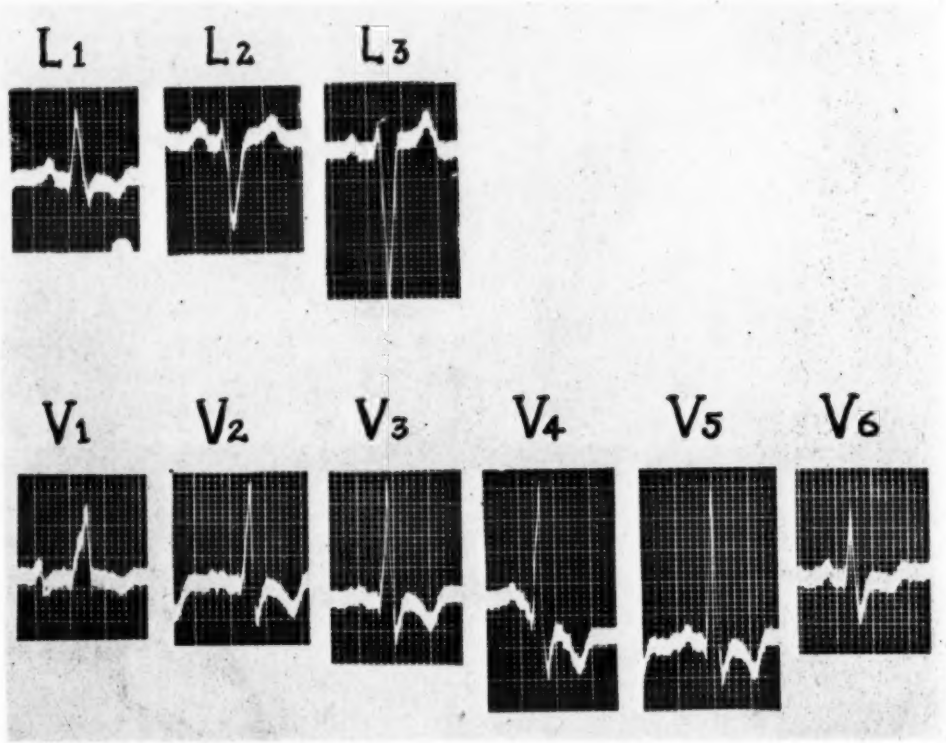
The results of our studies in five patients with left bundle branch block are listed in Table V. The history strongly suggested myocardial infarction in all five, and we feel that the left bundle branch block obscured the electrocardiographic pattern of myocardial infarction so as to prevent electrocardiographic confirmation of the diagnosis of myocardial infarction. The very abnormal electrokymographic patterns of left ventricular pulsations provided evidence of areas of abnormally contracting muscle, perhaps areas of myocardial infarction.

DISCUSSION

There has been a great deal of experimental work done on the changes in myocardial contractility secondary to myocardial infarction.[19-22] Tenant and Wiggers[22] studied the effect of coronary occlusion on myocardial contractility systematically. By means of a myograph and Frank capsule placed over the involved area, these authors recorded myocardial contractions and noted a progressive enfeeblement of ventricular contractions with a reversal of the normal myographic pattern after myocardial infarction. Murray[23] noted dilation of ventricular muscle, lack of contractility, and systolic paradoxical ballooning



A.



B.

Fig. 7.—*A* shows the curves of F.Y., Table IV. Abnormal pulsations, discussed in the text, are noted in the lower two curves. *B*, The electrocardiogram shows right bundle branch block without evidence of myocardial infarction.

TABLE V. GROUP E: CASES SHOWING PARADOXICAL PULSATION OF THE LEFT VENTRICLE WITH SUPPORTIVE CLINICAL FINDINGS: ELECTROCARDIOGRAM PATTERN OBSCURED BY LEFT BUNDLE BRANCH BLOCK

	NAME	DIAGNOSIS	PARADOXICAL PULSATION FLUOROSCOPICALLY	ELECTROKYMOGRAM	
				SYSTOLIC	DIASTOLIC
1	A. B.	ASHD	Paradoxical lower one-fourth left ventricle in PA		Mid and late diastolic collapse
2	T. N.	Hyp. ASHD	Paradoxical lower one-half left ventricle in PA	Early expansion	Collapse
3	M. R.	Hyp. ASHD	Paradoxical mid one-third left ventricle in PA	Mid-systolic expansion	Collapse
4	G. H.	ASHD	Paradoxical in PA	Early expansion	Collapse
5	C. F.	ASHD	Paradoxical in PA	Early expansion	Collapse

ASHD = Arteriosclerotic heart disease.
Hyp. ASHD = Hypertensive arteriosclerotic heart disease.
PA = Posteroanterior position.
EKY = Electrokymogram.
ECG = Electrocardiogram.

after tying off a major coronary vessel in animals. Prinzmetal and co-workers[24] noted that "it is well known clinically and experimentally that an ischemic portion of myocardium may bulge or 'balloon' during systole." These latter investigators studied myocardial contractions in thirty anesthetized dogs by means of slow-motion color pictures after exposure of the heart and ligation of the anterior descending branch of the left coronary artery. Coronary ligation was followed by "ballooning" out (on systole) of the ischemic myocardium. This change was noted in ten to twelve beats after ligation, at which time even the ischemic region was observed to contract in systole and not to balloon until later in systole—late systolic expansion. Frequently, however, the ballooning phenomenon became more prolonged until it occupied the whole of systole.

Several fluoroscopic and roentgenkymographic studies of myocardial contraction after myocardial infarction have been done. Master and associates[25] studied ninety-five cases fluoroscopically (fifteen with angina pectoris, eighty with myocardial infarction) and noted evidence of systolic expansion in 50 per cent and diminished or absent pulsations in another 23 per cent. It is of interest to note that Master and associates[25] found that abnormal left ventricular pulsations were best seen in the posteroanterior position after anterior wall infarction, while abnormal pulsations were seen equally well in the posteroanterior and left oblique positions after posterior wall infarction. These latter investigators concluded that fluoroscopy could not be relied upon to localize the area of myocardial infarction. Sussman and co-workers[3,4] studied eighty-five cases of recent myocardial infarction (less than two months in duration) with the roentgenkymograph and found definite abnormalities in 75 per cent. These included: (1) diminution or absence of pulsation in a localized segment of the left ventricular contour; (2) systolic expansion, either partial in early systole or complete throughout systole; and (3) marked diastolic splintering or other irregularities in diastole. Sussman and his co-workers also noted that both anterior and posterior myocardial infarction tended to produce roentgenkymographic abnormalities mostly

in the posteroanterior position. Only infrequently were such abnormalities noted in the left oblique position, and these were in instances of posterior wall myocardial infarction.

Gubner and Crawford[2] studied forty-five cases of myocardial infarction by the roentgenkymograph in the posteroanterior and both oblique positions. In forty-one cases the kymogram was abnormal. In twenty-five cases the roentgenkymogram and the electrocardiogram corresponded exactly as to localization, but in three cases the roentgenkymogram was normal while the electrocardiogram showed posterior wall infarction. Thomas and Garland[26,27] have also studied cases of myocardial infarction with the roentgenkymogram and noted noncontractile regions on the left ventricular borders. Several studies have appeared in which the electrokymogram was used to record left ventricular pulsations after myocardial infarction.[12-17] Luisada and Fleischner[16] listed nine types of major ventricular electrokymographic abnormalities which they found in twenty cases of myocardial infarction. Only two of these, lack of pulsation and paradoxical pulsation, were felt to be diagnostic of localized myocardial damage.

Various types of abnormal left ventricular pulsations have been noted in our cases. These may be divided into two groups which include systolic expansion and diastolic collapse patterns.

Systolic patterns include: (1) early systolic expansion; (2) mid-systolic expansion; (3) late systolic expansion; and (4) a flat curve in systole, neither expansion nor contraction noted on the electrokymographic curve.

Examples of these types have been illustrated in the figures above. The commonest type we have observed is early systolic expansion. Because of the torsional and rotational factors involved in the formation of the left ventricular electrokymogram and because of the relative ease with which a delayed onset of the left ventricular downstroke may be produced by a minimally incorrect placing of the pickup unit over the ventricular border, we feel that the use of delayed onset as a criterion of abnormal pulsation[35] is open to question.

The diastolic patterns include: (1) early diastolic collapse; (2) mid-diastolic collapse; and (3) late diastolic collapse.

The most frequent type of diastolic abnormality has been the early diastolic collapse.

It is our belief that these various types of abnormal ventricular movements have a similar underlying etiological factor which is related to the varying levels of intraventricular pressures in the cardiac cycle. Early systolic expansion is occasioned by poor contractility of the involved muscle so that even the relatively low early intraventricular pressure will be enough to balloon out the region of abnormal musculature. Mid and late systolic expansion suggests that the abnormal muscle had sufficient strength to withstand the relatively low intraventricular pressure in early systole, but with the development of higher intraventricular pressures later in systole, expansion takes place. A region of muscle that is expanded in systole will, of course, collapse in diastole with a fall of intraventricular pressure. The reason for the various types of abnormal diastolic collapse remains somewhat obscure. We have little evidence upon which to

base opinions as to the prognostic significance, if any, of each of these different systolic and diastolic abnormalities.

Review of our over-all results reveals several points of interest. Fluoroscopic evidence of abnormal paradoxical pulsation was noted in forty-eight of seventy cases, or in approximately two of every three cases. In line with this finding is the study reported by Wang and associates,[28] in which it is said that "aneurysmal concavities of small degree are commonly present" after myocardial infarction. Electrokymographic evidence of abnormal paradoxical pulsation was noted in fifty-four of seventy cases or approximately three of every four cases. While there is no doubt that the electrokymogram will detect instances of paradoxical pulsation not seen even by an experienced fluoroscopist, we would like to stress the value of careful cardiac fluoroscopy in finding abnormal ventricular pulsations. By timing ventricular pulsations with the aid of great vessel pulsations, one can soon become quite adept at picking up abnormal pulsations quickly. Another point worthy of stress is that left ventricular paradoxical pulsations after myocardial infarction are noted best on both the fluoroscope and the electrokymogram in the posteroanterior position, irrespective of whether the electrocardiogram localizes the myocardial infarction to the anterior or posterior wall. Thus in the group of anterior wall infarctions, there was 100 per cent correlation between the electrocardiographic and electrokymographic sites of infarction. In the group of posterior wall infarction, twelve of twenty-eight cases did not show correlation between the electrokymographic and electrocardiographic sites of infarction. In the series of combined anterior and posterior wall myocardial infarction, complete correlation between the electrocardiogram and electrokymogram was present in only five of eleven cases. That is, only five of eleven cases showing anterior and posterior infarction on the electrocardiogram showed paradoxical pulsation on the electrokymogram in both the posteroanterior and left oblique positions. It thus appears that correlation between the electrocardiogram and the electrokymogram is only fairly good at best, especially in patients with posterior wall infarction. Master and co-workers[25] have had similar experiences in attempting to correlate the electrocardiographic and fluoroscopic sites of paradoxical pulsations. The fact that most left ventricular aneurysms are of the anterior wall rather than the posterior wall[29] at post-mortem examination is also in line with our findings.

It is our feeling that the finding of paradoxical pulsations on the fluoroscope or electrokymogram does not permit one to conclude that myocardial infarction has occurred. As we have noted above, in ten cases of enlarged hearts due to various causes paradoxical pulsations occurred without myocardial infarction. In three of these ten cases myocardial infarction was absent at post-mortem examination. From this experience we have concluded that ischemic, non-infarcted myocardium (in a markedly enlarged heart) may contract abnormally or not at all and result in abnormal pulsations on the fluoroscope or electrokymogram. We do not find ourselves in agreement with the statement made by Sussman and associates[35] that "with rare exceptions such findings indicate antecedent myocardial infarction or ventricular aneurysm." Gillick[36] has also observed paradoxical left ventricular pulsations "in patients with neither an electrocardiogram nor a clinical history indicative of myocardial infarction."

The electrokymogram may be of great aid in supporting the diagnosis of myocardial infarction in the presence of left bundle branch block. It is well known[30-34] that the diagnosis of myocardial infarction, especially anterior wall myocardial infarction, is difficult in the presence of left bundle branch block. The presence of abnormal ventricular pulsations may be of aid in confirming the diagnosis of myocardial infarction in cases of left bundle branch block. Of course, in this regard one must keep in mind the fact that paradoxical pulsations may be present in enlarged hearts without myocardial infarction.

SUMMARY

A study of the incidence of paradoxical pulsations, both fluoroscopic and electrokymographic, has been made in thirty-one cases of anterior wall infarction, in twenty-eight cases of posterior wall infarction, and in eleven cases of combined anterior and posterior infarctions. The types of paradoxical pulsations noted have been listed. The presence of paradoxical pulsations without myocardial infarction has been noted, together with mention of the possible aid that the electrokymograph may give in the diagnosis of myocardial infarction in the presence of left bundle branch block.

We are indebted to Dr. Arthur C. DeGraff, Senior Consultant to the Medical Service, V. A. Hospital, Bronx, N. Y., for aid and encouragement which made this work possible.

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ELECTROKYMOGRAPHIC STUDIES OF THE RELATION BETWEEN THE ELECTRICAL AND MECHANICAL EVENTS OF THE CARDIAC CYCLE IN WOLFF-PARKINSON-WHITE SYNDROME

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NEW YORK, N. Y.

INTRODUCTION

STUDIES of possible correlation between the electrical and mechanical events of the cardiac cycle date back to the pioneer work of Wiggers[1,2] and Lewis.[3] These investigators were concerned with the relationships between the electrocardiogram and such variables as heart sounds, peripheral arterial and venous pulse curves, and intracardiac pressure curves.

The discovery of the phenomenon of pre-excitation as exemplified by the syndrome of anomalous atrioventricular excitation (Wolff-Parkinson-White syndrome) has produced fertile soil for detailed studies of the relations between electrical and mechanical cardiac asynchronism. Although similar isolated cases were described by Wilson,[4] Wedd,[5] and Hamburger,[6] it was Wolff, Parkinson, and White[7] who first clearly defined the curious electrocardiographic and clinical patterns present in this syndrome of a short P-R interval and a prolonged QRS complex.

The concept of an accessory atrioventricular pathway similar to the bundle of Kent[8] was first advocated by Holtzmann and Scherf[9] and Wolferth and Wood[10] and still represents the most acceptable explanation of this pattern to date. The experimental studies of Butterworth and Poindexter,[11] in which the electrocardiographic pattern of a short P-R and a prolonged QRS was produced in cats and dogs by means of a special amplifier which picked up and amplified the potential generated by the auricular muscle and which short-circuited the normal conduction system of the heart by directly stimulating the ventricles to premature excitation by means of this amplified auricular potential, produced strong evidence for such a bundle of Kent hypothesis. The amplifier was said to act as did the accessory bundle. The fact that paroxysmal tachycardia could be produced in these experiments by merely reversing the direction of current flow in the amplifier was further proof.

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the results of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Received for publication March 24, 1950.

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Histologic support for the above thesis was forthcoming in the studies of Glomset and Glomset,[12] Wood, Wolferth, and Geckeler,[13] and Ohnell.[14] The Glomsets studied the cardiac conduction system in various mammals and found many muscle bridges other than the bundle of His connecting the auricles and ventricles in human hearts. Wood and co-workers[13] studied a teen-aged boy in a mental institution who clinically had an electrocardiogram of the Wolff-Parkinson-White category and who died during a bout of tachycardia. Careful multiple sections about the A-V groove were made and three muscle bundles were found on the right lateral border of the heart with at least two of these connecting the right auricle and right ventricle directly. The electrocardiographic pattern resembled that of left bundle branch block. Ohnell[14] has reported a case in which the electrocardiogram during life revealed a Wolff-Parkinson-White picture, and multiple sections at post-mortem examination showed in addition to an apparently normal bundle of His, a muscle bundle 6 mm. in length connecting the left auricle with the left ventricle.

Pharmacologic support for the thesis of an anomalous atrioventricular connection was obtained by Roberts and Abramson.[15] These investigators noted that quinidine changed an electrocardiogram showing a Wolff-Parkinson-White syndrome to normal and postulated that quinidine inhibited conduction along the accessory pathway. In their original study, Wolff, Parkinson, and White[7] noted that exercise and atropine (both producing antivagal effects) could result in restoration of a Wolff-Parkinson-White pattern to a normal pattern and that vagal stimulation then resulted in a return to the Wolff-Parkinson-White pattern. Since this can be restated to note that vagal stimulation resulted in a shortening of the P-R interval (when the Wolff-Parkinson-White pattern was reestablished) instead of a prolongation of the P-R interval as more often occurs, the results of vagal stimulation were originally regarded as paradoxical. With the bundle of Kent hypothesis in mind, however, one can say that vagal stimulation results in delay of the impulse at the A-V node more than at the bundle of Kent and thus explain the above results.

Despite the simplicity and attractiveness of the bundle of Kent hypothesis, a number of investigators have expressed dissatisfaction with this theory. Two detailed studies[14,16] discussing other possible electrocardiographic mechanisms of production of this syndrome have been published. These include: (a) hypothesis accepting the Wolff-Parkinson-White syndrome as a true bundle branch block, (b) hypothesis of increased conductivity of one bundle branch, (c) hypothesis of mechanical excitation of an irritable ventricular focus by auricular systole, and (d) hypothesis of ventricular extrasystoles interfering with a normal sinus beat with production of a fusion beat. Ohnell[14] and Mahaim[17] have challenged the histologic evidence upon which the bundle of Kent thesis is based. Despite these objections, however, most cardiologists still feel that the bundle of Kent hypothesis is the most likely explanation of the various phenomena that have been observed.

Implicit in the concept of a bundle of Kent is pre-excitation, electrically at least, of one ventricle compared to the other. If there is a muscular connection other than the bundle of His between auricle and ventricle on either side, it follows

that one ventricle will receive the stimulus for depolarization ahead of the other, even though the depolarization may be along an abnormal pathway instead of along the Purkinje fiber system. In many instances of the Wolff-Parkinson-White syndrome a fusion beat may be produced by fusion of the depolarization wave from the bundle of Kent with the depolarization wave spreading from the normal (although delayed as compared to the anomalous) pathway along the bundle of His and bundle branches. The theory of electrical pre-excitation suggests the possibility of mechanical ventricular asynchronism with the lag in ventricular contraction and ejection on the side opposite the anomalous bundle. Since Burch and Kimball[18] have published tracings of this syndrome simulating both right and left bundle branch block, it follows that the bundle of Kent may be on either the left or right side and that, therefore, mechanical asynchronism with the delay of ejection from either the right or left ventricle is at least a theoretical possibility if correlation between the electrical and mechanical events of the cardiac cycle occurs.

The actual evidence for and against ventricular mechanical asynchronism in Wolff-Parkinson-White syndrome is inconclusive. The actual or possible occurrence of mechanical ventricular asynchronism has been maintained by Butterworth and Poindexter,[11] Wolferth and Wood,[10,19] Wood, Wolferth, and Geckeler,[13] Wolff, Parkinson, and White,[7] Cosseo and co-workers (quoted by Ohnell[14]), Scherf and Schonbrunner,[20] and Zarday (quoted by Ohnell[14]). Moia and Inchauspe[21] studied one case in which normal beats (P-R, 0.16; QRS, 0.06) alternated with Wolff-Parkinson-White complexes (P-R, 0.09; QRS, 0.12). Records were made simultaneously of the electrocardiogram, venous and arterial pulse waves, and phonocardiogram. The tracings showed mechanical ventricular asynchronism with the right ventricle ahead of the left when the electrocardiogram suggested a right bundle of Kent. Reindell and Bayer[22] measured the interval from the onset of the QRS to the onset of the carotid pulse in a similar case and also felt that mechanical asynchronism had been demonstrated.

Other observers doubt the occurrence of asynchronism. This group includes Eckey and Schafer,[23] who studied one case with recordings of electrocardiogram, heart sounds, and venous and arterial pulse curves; Feldmann and Koch,[24] Hunter, Papp, and Parkinson,[16] Gruber,[25] Wunche,[26] and Spangenberg, Vendoya, and Gonzalez,[27] who recorded the electrocardiogram, heart sound, and arterial and venous pulse curves in one case.

More recently two excellent studies have been done in this country. Kossman and Goldberg[28] studied a patient who showed normal beats alternating with Wolff-Parkinson-White complexes on the electrocardiogram. The Q-E inte val (defined as the interval from the onset of the QRS complex to the onset of the carotid pulse wave in the neck) measured 0.15 second for the normal beats and 0.202 second for the Wolff-Parkinson-White beats. These data were compared to similarly obtained data in normals and cases of right and left bundle branch block. On this basis, the authors stated that there was asynchronous contraction of the ventricles. One objection to their conclusions must be mentioned. The data indicated only delayed ejection from the left side of the heart. No

studies of right-sided ventricular ejection were done, and the possibility of delayed ejection from the right ventricle at the same time was not considered. Obviously, if there was delayed right-sided ejection, ventricular asynchronism might not have been present despite the evidence for prolonged Q-E interval on the left side. This point has been raised because of a study done by Ferrer and associates[29] on two cases of Wolff-Parkinson-White syndrome in which cardiac catheterization was performed and the interval from the onset of the QRS to the onset of the right ventricular systolic pressure rise could be measured. A peripheral arterial pulse curve was simultaneously obtained with an indwelling needle in the brachial artery. With this technique it was noted that in one patient who showed a right bundle branch block pattern (therefore suggesting a left bundle of Kent), there was delay in ejection from both sides of the heart, right and left, despite and left-sided bundle of Kent. That is, the interval from the QRS to the onset of the right ventricular pressure curve and to the onset of the brachial artery pressure rise was prolonged in both instances, thereby proving delayed right and left ventricular ejection. In a second patient with an electrocardiographic pattern suggesting left bundle branch block (and, therefore, a right bundle of Kent), left ventricular ejection was markedly delayed while right ventricular contraction was only slightly delayed. Again, there is evidence of delay on both sides of the heart. One can thus not conclude that ventricular asynchronism is present merely because there is delayed ejection from one side of the heart.

The development of the electrokymogram[30-33] has allowed us to undertake a study correlating the electrical and mechanical events of the cardiac cycle in fifteen cases of Wolff-Parkinson-White syndrome.

CLINICAL DATA

The pertinent clinical data are as follows:

Group B.—

CASE 1.—J. M. was a 43-year-old white man who had noted recurrent bouts of tachycardia over at least the past five years. A superimposed anxiety neurosis was also present. Physical examination of the cardiovascular system was noncontributory.

CASE 2.—H. C. was a 23-year-old white man with bouts of paroxysmal tachycardia over "many years." History and physical examination were otherwise noncontributory.

CASE 3.—W. B. was a 35-year-old white man with bouts of paroxysmal tachycardia as his only complaint. Physical examination was noncontributory.

CASE 4.—R. D. was a 35-year-old white man without any complaints except for bouts of paroxysmal tachycardia. Physical examination was negative.

CASE 5.—W. S. was a 30-year-old white man with bouts of paroxysmal tachycardia. History and physical examination were otherwise noncontributory.

CASE 6.—C. S. was a 27-year-old white man with rheumatic heart disease, enlarged heart, mitral stenosis and insufficiency, and aortic insufficiency. He was treated twice for subacute bacterial endocarditis. Sinus rhythm was present. The patient was not given digitalis.

CASE 7.—F. L. was a 52-year-old white man with no heart disease. He had no history of bouts of paroxysmal tachycardia.

CASE 8.—B. K. was a 63-year-old white man with no cardiovascular complaints. Physical examination was noncontributory.

Group A.—

CASE 1.—F. R. was a 53-year-old white man with arteriosclerosis obliterans of the left lower extremity. Blood pressure was normal. Cardiac status was normal except for the presence of a Wolff-Parkinson-White syndrome.

CASE 2.—M. M. was a 73-year-old white man with arteriosclerotic heart disease and a duodenal ulcer. The heart was not enlarged. Blood pressure was 150/70 mm. Hg.

CASE 3.—A. P. was a 62-year-old white man with hypertensive and arteriosclerotic heart disease with an enlarged heart. Cardiac failure was absent. Blood pressure was 160/110 mm. Hg.

CASE 4.—S. S. was a 38-year-old white man complaining of bouts of paroxysmal tachycardia. History and physical examination were otherwise noncontributory.

CASE 5.—C. L. was a 37-year-old white man complaining of bouts of paroxysmal tachycardia. History and physical examination were otherwise negative.

CASE 6.—F. L. was a 53-year-old white man with hypertensive and arteriosclerotic heart disease. Cardiac enlargement was present. Blood pressure was 190/105 mm. Hg. Cardiac failure was absent.

CASE 7.—F. B. was a 44-year-old white man. Bouts of paroxysmal tachycardia constituted the only complaint.

It should be noted that: (1) None of the patients was given digitalis or was in failure. (2) Eight patients had apparently normal hearts with bouts of paroxysmal tachycardia. Two patients had normal hearts without bouts of tachycardia. One had a normal heart with arteriosclerosis obliterans of the lower extremity. Two had hypertensive and arteriosclerotic heart disease and one had arteriosclerotic heart disease. One patient was suffering from rheumatic heart disease. (3) In two cases the QRS complex measured only 0.10 second. Since the P-R intervals were 0.10 and 0.11 second in these cases and since the P waves in Leads II and III were upright, we felt justified in including them in the series of Wolff-Parkinson-White cases.

TECHNIQUE

The electrokymograph is an instrument for recording heart border motions utilizing a photoelectric cell placed between the patient and the fluoroscopic screen with the roentgenoscopic beams as the source of energy. Variations in the amount of radiation reaching this cell occur as the heart expands in diastole and contracts in systole. This variation can be recorded after passage through a suitable power box. We have recorded electrokymograms of the ascending aorta and pulmonary artery simultaneously in the right anterior oblique position, with the patient sitting on a low stool. In this position on the anterior border of the heart, the ascending aorta and, just below, the pulmonary artery could easily be seen, and the photoelectric cells were placed at the border of these structures so as to allow for simultaneous electrokymographic recordings of their pulsations. We have recorded an electrocardiogram simultaneously with the two electrokymograms on a three-channel direct-writing Technicon. A direct-writing apparatus allows for immediate visualization of our results and immediate repetition of any unsatisfactory curves. Simultaneous recording of the electrokymograms of the two great vessels permits a direct comparison of the curves without the necessity for using the carotid artery pulse wave as a reference point as is usually done. The accuracy of our measurements is thereby greatly improved. Preliminary to the present study we recorded electrokymograms of

the two great vessels in more than fifty normals to establish our range of normality. This varied from plus 0.03 to minus 0.02 second. That is, the pulmonary artery ejection phase (as measured by the sharp upstroke of this curve at the end of the isometric contraction phase) might precede the corresponding ejection phase of the ascending aorta by 0.03 second or follow it by as much as 0.02 second. As noted above, we have made these studies in fifteen cases of Wolff-Parkinson-White syndrome, in an attempt to note whether electrical asynchronism or pre-excitation would be accompanied by mechanical asynchronism or pre-excitation.

RESULTS

Following the classification set up by Rosenbaum and co-workers,[34] we have divided our cases into Group A and Group B. In the former group the R wave is the sole or largest deflection of the QRS complex in leads from the right side of the precordium. In Group B, on the other hand, the QRS complex shows an S or a QS as the chief deflection in leads from the right side of the precordium. We have found that in Group A the greatest delay in the intrinsicoid deflection occurs in leads from the right side of the precordium, suggesting the pattern of right bundle branch block and a left-sided bundle of Kent. In Group B the greatest delay in the intrinsicoid deflection occurs in leads from the left side of the precordium, suggesting the pattern of left bundle branch block and a right-sided bundle of Kent.

Table I shows our results in twenty-five normals. In these twenty-five patients the average relation between the pulmonary artery and ascending aorta was 0.00, the two sides of the heart ejecting blood at approximately the same time. The interval between the onset of the QRS and the upstrokes of the pulmonary artery and ascending aorta averaged 0.118 second. Except in Cases 3, 4, and 11, the time interval between the onset of the QRS and the onset of ejection from either side of the heart, as measured by onset of ejection on the electrokymograms of the two great vessels, is less than 0.15 second.

In Table II the results of electrokymographic studies of this problem are shown in seven patients, all in Group A, in which the R is the sole or largest deflection of the QRS in leads from the right side of the precordium. In four of these patients the relation of the upstrokes of the pulmonary artery and ascending aorta was within normal limits. That is, there was no correlation between the presence of electrical pre-excitation as suggested by the electrocardiogram and mechanical ventricular asynchronism. In three instances the relations were such that the ascending aorta upstroke was abnormally ahead of the pulmonary artery. Correlation was thus present in less than half of the cases. However, if we examine the figures for the interval between the onset of the QRS and the beginning of ascending aorta and pulmonary artery ejection, quite another story unfolds. It is easily seen that there is delayed mechanical ejection from both sides of the heart in both groups of patients. There is delayed mechanical ejection from both sides of the heart whether or not mechanical ventricular asynchronism is present. In all seven patients ejection from the right side is uni-

TABLE I. NORMALS

CASE	NAME	RELATION PUL. A.* AND ASC. A.	QRS TO ASC. A.	QRS TO PUL. A.
1	J. C.	−0.02	0.09	0.11
2	A. C.	0.03	0.13	0.10
3	K. J.	0.01	0.16	0.15
4	J. M.	−0.02	0.15	0.17
5	W. S.	0.03	0.11	0.08
6	W. F.	−0.02	0.13	0.15
7	B. S.	−0.02	0.12	0.14
8	U. P.	0.02	0.13	0.11
9	C. R.	−0.02	0.11	0.13
10	R. D.	0.00	0.12	0.12
11	R. S.	−0.02	0.14	0.16
12	S. B.	0.02	0.14	0.12
13	W. S.	−0.01	0.10	0.11
14	J. D.	−0.02	0.09	0.11
15	F. R.	0.02	0.12	0.10
16	D. F.	0.03	0.11	0.08
17	A. F.	0.01	0.10	0.09
18	E. W.	0.01	0.11	0.10
19	J. S.	−0.02	0.12	0.14
20	S. R.	0.02	0.13	0.11
21	F. P.	−0.01	0.11	0.12
22	W. S.	0.00	0.10	0.10
23	A. B.	−0.01	0.10	0.11
24	S. K.	0.00	0.13	0.13
25	J. N.	−0.01	0.11	0.12
Average		0.000	0.118	0.118

*A minus sign means the ascending aorta is ahead of the pulmonary artery.

TABLE II. GROUP A: WOLFF-PARKINSON-WHITE SYNDROME, LEFT BUNDLE OF KENT

CASE	NAME	P-R	QRS	RELATION PUL. A.* AND ASC. A.	CORRELATION	QRS TO ASC. A.	QRS TO PUL. A.
1	F. R.	0.09	0.12	−0.01	No	0.17	0.18
2	M. M.	0.10	0.12	0.01	No	0.17	0.16
3	A. P.	0.09	0.13	0.01	No	0.20	0.19
4	S. S.	0.06	0.14	−0.02	No	0.18	0.20
Average				−0.003		0.180	0.182
5	C. L.	0.08	0.11	−0.04	Yes	0.14	0.18
6	F. L.	0.08	0.12	−0.04	Yes	0.14	0.18
7	F. B.	0.08	0.13	−0.06	Yes	0.11	0.17
Average				−0.05		0.130	0.177

*A minus sign means the ascending aorta is ahead of the pulmonary artery.

formly delayed with an average QRS to pulmonary artery upstroke time of 0.18 second. In the first four patients left-sided ventricular ejection is delayed proportionately to the right side, despite the presence of earlier electrical activation of the left ventricle. In the remaining three patients, this delayed ejection

from the left ventricle is much less marked, with only slight but definite delay of left ventricular ejection. Comparison with the normal figures will show some overlapping in the latter three cases, but the average figures show distinct differences in all instances.

In Table III the results of study of the eight cases of Group B are shown. In this division the electrocardiogram showed predominantly an S or QS deflection of the QRS in leads from the right side of the precordium suggesting a right-sided bundle of Kent. In six cases there is no mechanical asynchronism as noted by a normal relation between the onset of ejection in the pulmonary artery and ascending aorta. In two cases the pulmonary artery is minimally ahead of the ascending aorta. Again, in all eight patients there is delayed ejection from both ventricles regardless of the presence or absence of mechanical asynchronism. In this table the patients in both subdivisions show marked delay of ejection from the left ventricle. Those in the first subdivision show marked delay of ejection from the right ventricle, but the two patients in the second subdivision show only minimal delay of right ventricular ejection. Again, comparison with the normal figures shows some overlapping, especially in the last two cases.

In Table III please note Case 1 and Case 6. In both of these instances there is an abnormal relation between the onset of pulmonary artery and ascending aorta ejection, but in a direction opposite to that expected. In both instances the ascending aorta is 0.04 second ahead of the pulmonary artery, yet the electrocardiogram suggests a right-sided bundle of Kent. Again, clearly, correlation between the electrical and mechanical does not occur.

TABLE III. GROUP B: WOLFF-PARKINSON-WHITE SYNDROME, RIGHT BUNDLE OF KENT

CASE	NAME	P-R	QRS	RELATION PUL. A.* AND ASC. A.	CORRELATION	QRS TO ASC. A.	QRS TO PUL. A.
1	J. M.	0.10	0.10	−0.04	No	0.15	0.19
2	H. C.	0.11	0.10	0.02	No	0.20	0.18
3	W. B.	0.08	0.12	0.03	No	0.18	0.15
4	R. D.	0.10	0.12	0.01	No	0.13	0.12
5	W. S.	0.09	0.12	−0.03	No	0.17	0.20
6	C. S.	0.10	0.15	−0.04	No	0.16	0.20
Average				−0.009		0.165	0.173
7	F. L.	0.08	0.11	0.04	Yes	0.18	0.14
8	B. K.	0.08	0.12	0.04	Yes	0.17	0.13
Average				0.04		0.175	0.135

*A minus sign means the ascending aorta is ahead of the pulmonary artery.

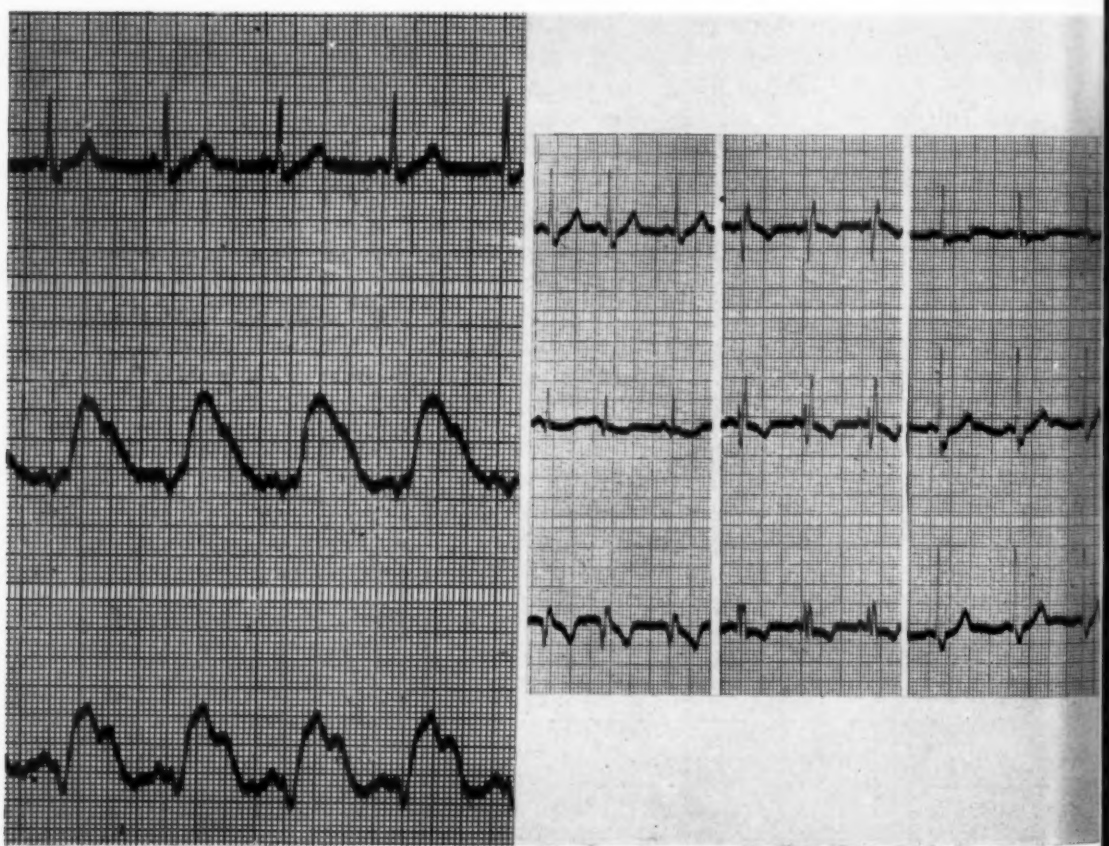
Examples of the curves upon which our data are based appear in Figs. 1 to 6.

Fig. 1 shows the results in M. M. of Group A. The left side shows a tracing of Lead I, the ascending aorta and the pulmonary artery from above down. The latter is 0.01 second ahead of the former. The right half of the figure shows the electrocardiogram.

Fig. 2 shows the results in S. S. of Group A. The left side shows a tracing of Lead I, ascending aorta and pulmonary artery from above down. The relation here is minus 0.02. The right half of the figure shows the electrocardiogram.

Fig. 3 shows the results in C. L., Group A. To the left is a tracing of Lead II, ascending aorta, and pulmonary artery. The relation is minus 0.04 and correlation is thus present with the ascending aorta abnormally ahead of the pulmonary artery. To the right is the electrocardiogram.

Fig. 4 shows the results in F. B., Group A. To the left is a tracing of Lead I, ascending aorta and pulmonary artery. The relation is minus 0.06 and again correlation is present with the ascending aorta abnormally ahead of the pulmonary artery. To the right is the electrocardiogram.



A. B.

Fig. 1.—M. M., Group A.

A, The electrokymogram: The upper curve is Lead I; the middle curve, the electrokymogram of the ascending aorta; and the lower curve, the electrokymogram of the pulmonary artery. The latter is 0.01 second ahead of the former, and the relation of the two is therefore within normal limits.

B, The electrocardiogram: To the left from above down are Leads I, II, and III. The middle section shows V_1, V_2, and V_3 from above down. The section to the right shows V_4, V_5, and V_6 from above down.

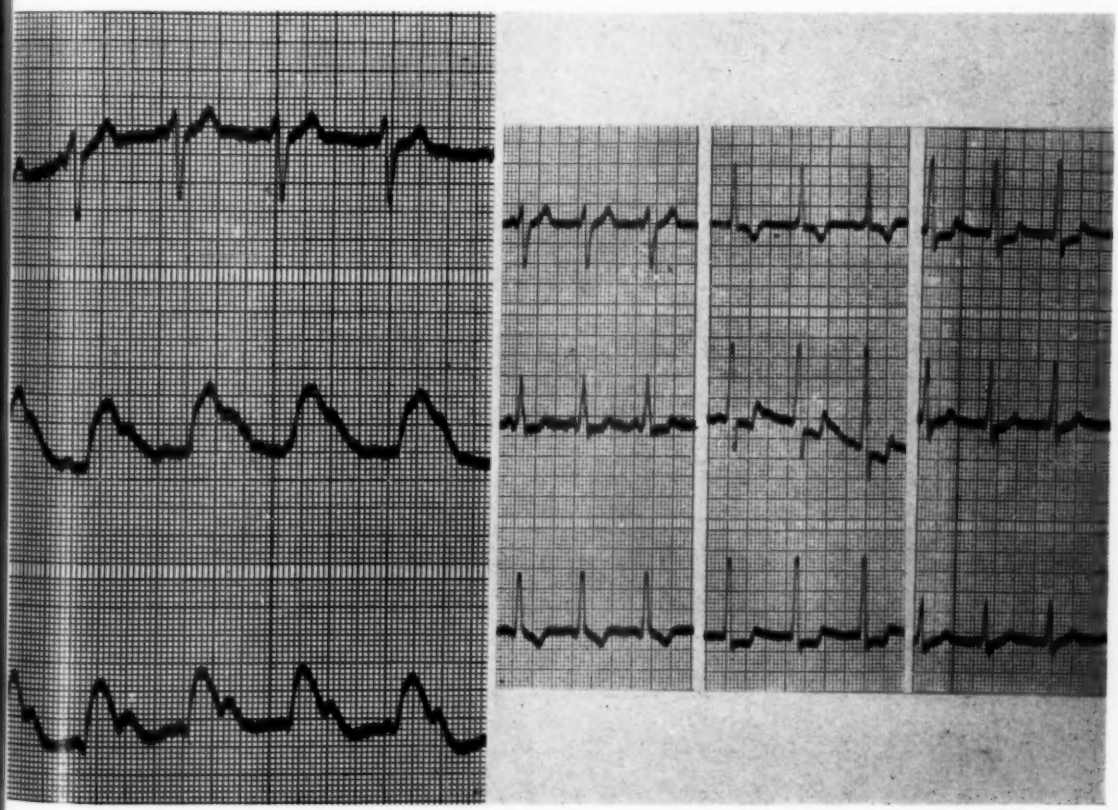
Fig. 5 shows the results in W. B., Group B. To the left is a tracing of Lead II, ascending aorta and pulmonary artery. The relation is 0.03. To the right is the electrocardiogram.

Fig. 6 shows the results in C. S., Group B. To the left is a tracing of Lead I, ascending aorta and pulmonary artery. The relation is minus 0.04. Despite the suggestion of a right bundle of Kent by the electrocardiogram, the ascending aorta is abnormally related to the pulmonary artery, but in a direction opposite to that expected. To the right is the electrocardiogram.

Repetition of the curves at different times has given similar results within the error of measurement of 0.01 second. The results are reproducible.

DISCUSSION

The results described above were rather unexpected yet it should be noted that Ferrer and associates[29] were led to similar conclusions by an entirely different



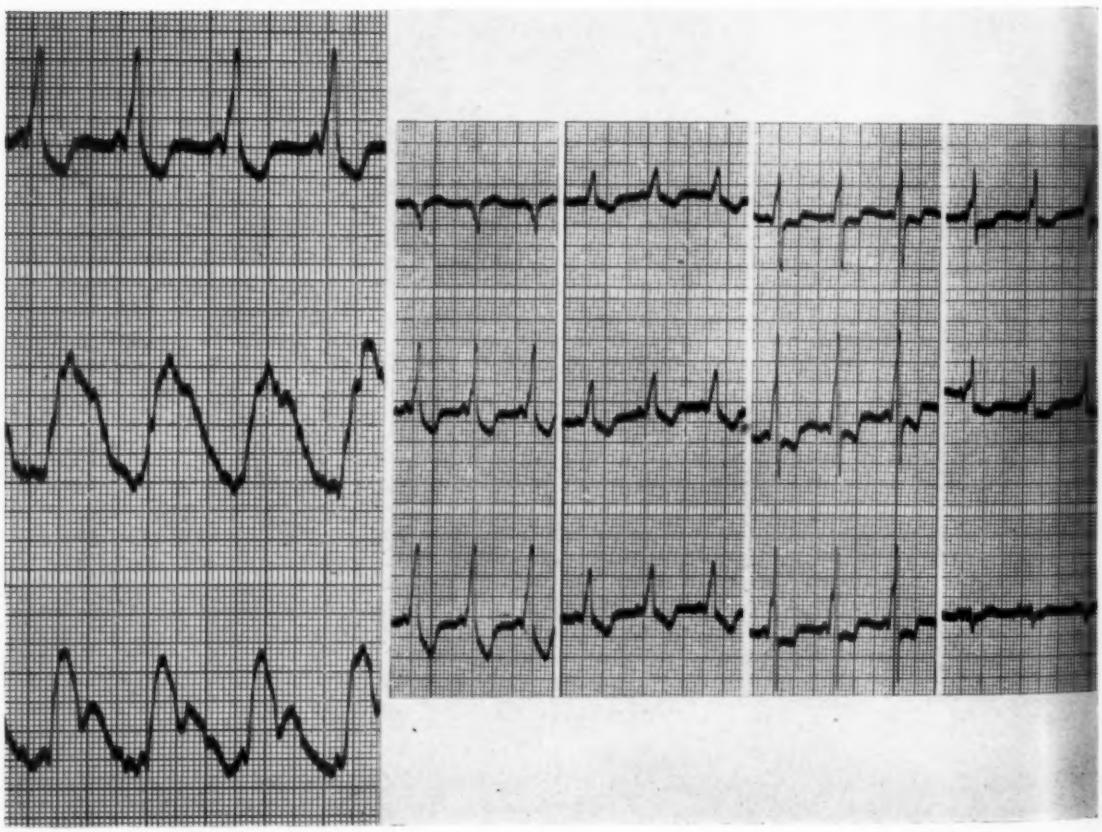
A. B.

Fig. 2.—S. S., Group A.

A, The electrokymogram: Lead I, ascending aorta and pulmonary artery from above down. The latter is 0.02 second behind the former, and the relation of the two is therefore within normal limits.

B, The electrocardiogram: To the left from above down are Leads I, II, and III. The middle section shows Leads V_1, V_2, and V_3 from above down. The section to the right shows V_4, V_5, and V_6 from above down.

experimental technique. It was originally believed that in the Wolff-Parkinson-White syndrome ventricular depolarization on the side of the bundle of Kent was initiated by that bundle, but that in the other ventricle depolarization was initiated through the normal conduction pathways (the His bundle and Purkinje system). This should result in early ventricular ejection on the side of the bundle of Kent and normal ejection from the other ventricle if correlation between the electrical and mechanical events of the cardiac cycle did occur. However, Ferrer and co-workers[29] found delayed ventricular ejection when this interval could be measured on both sides of the heart, regardless of the side of the bundle of Kent. The above-mentioned investigators, together with Kossman and Goldberg,[28] have felt that this situation alone indicates that the entire ventricular musculature is abnormally stimulated. Depolarization is said to start early on



A. B.

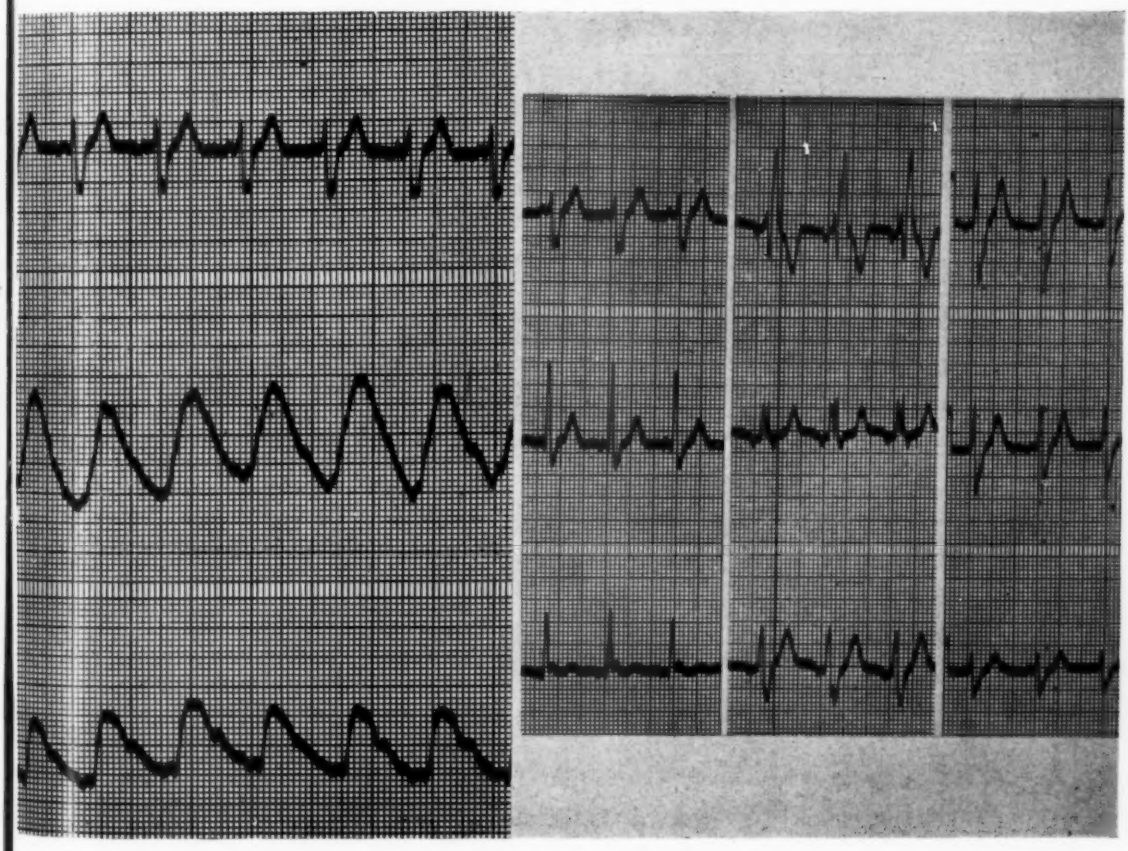
Fig. 3.—C. L., Group A.

A, The electrokymogram: Lead II, ascending aorta and the pulmonary artery from above down. The latter is 0.04 second behind the former. This relation is outside the normal range and therefore there is apparent correlation between the electrical and the mechanical events here.

B, The electrocardiogram: To the left are Leads I, II, and III from above down. The next section shows V_{R5}, V_{R4}, and V_{R3} from above down. The next section to the right shows V_2, V_3, and V_4 from above down. The section to the right shows V_5, V_6, and V_7 from above down.

the anomalous side and to spread through both ventricles directly, without use of the normal conduction system to any significant degree. While this thesis cannot be disproved, it seems to us that there is an alternative explanation for the results that have been obtained. The fact that there is delayed mechanical ejection from both ventricles does not mean that there is abnormal depolarization of both ventricles, unless one assumes that correlation between the electrical and mechanical events of the cardiac cycle occurs. There is some evidence that this is so,[35-38] but there is also evidence to the contrary.[39,40]

We have studied[41] eighty-three cases of bundle branch block, two cases of complete heart block with idioventricular rhythm, and fourteen cases of ventricular premature beats by the above technique and have found that mechanical ventricular asynchronism occurred in a minority of cases, despite the



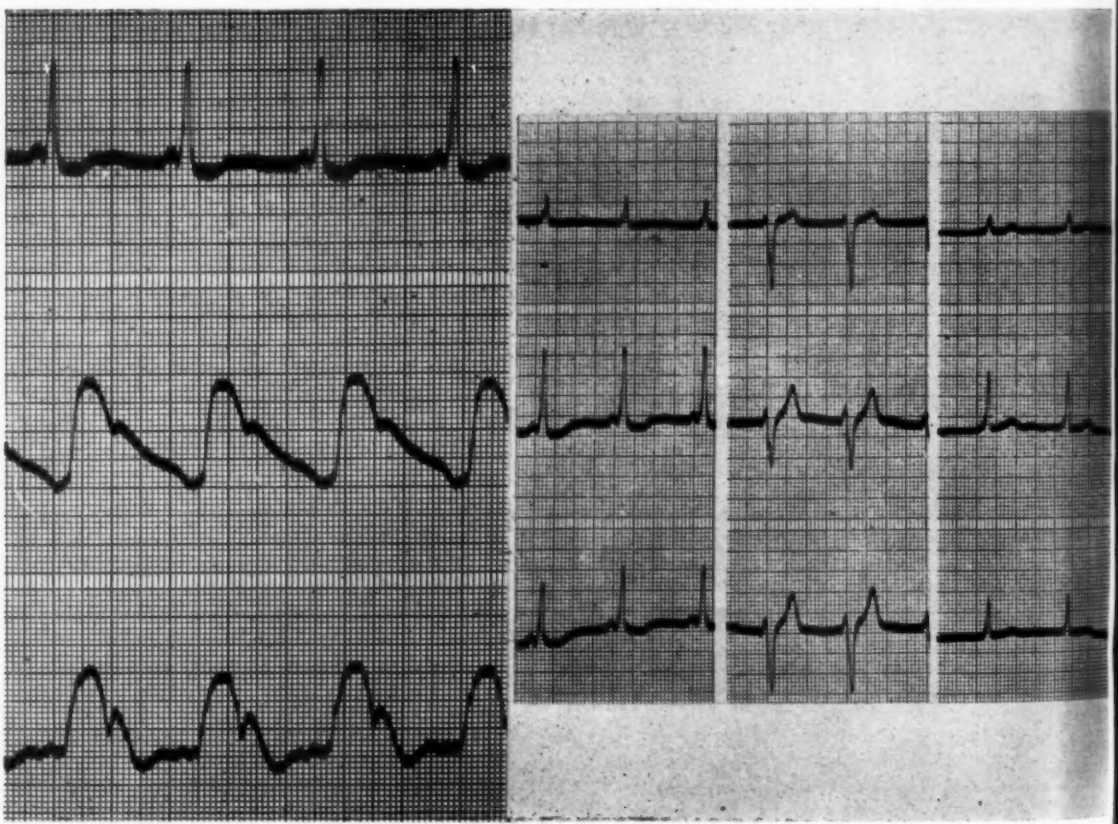
A. B.

Fig. 4.—F. B., Group A.

A, The electrokymogram: Lead I, ascending aorta and pulmonary artery from above down. The former is 0.06 second ahead of the latter. Here again there is apparent correlation between the electrical and mechanical events.

B, The electrocardiogram: To the left are Leads I, II, and III from above down. The middle section shows V_1, V_2, and V_3 from above down. To the right are Leads V_4, V_5, and V_6 from above down.

presence of electrical asynchronism in these ninety-nine cases. We, therefore, feel that data on mechanical ejection from the two ventricles should not be used to draw conclusions as to the pathways of electrical depolarization. Similarly it can be argued that our results, which show mechanical ventricular asynchronism in only five of fifteen cases of Wolff-Parkinson-White syndrome, can be interpreted to state that correlation between the electrical and mechanical events of the cardiac cycle does not occur since mechanical asynchronism did not accompany electrical asynchronism in most cases. Therefore, the possibility exists that the ventricle on the side opposite to the bundle of Kent is depolarized through the bundle of His despite delayed mechanical ejection on both sides. As noted above, of course, the alternate explanation advanced by Kossman and Ferrer cannot be denied. Indeed, Kossman's data on the arrival of the intrinsicoid deflection at the surface of the right and left ventricles in his case strongly suggest and support his hypothesis, at least in that one case.



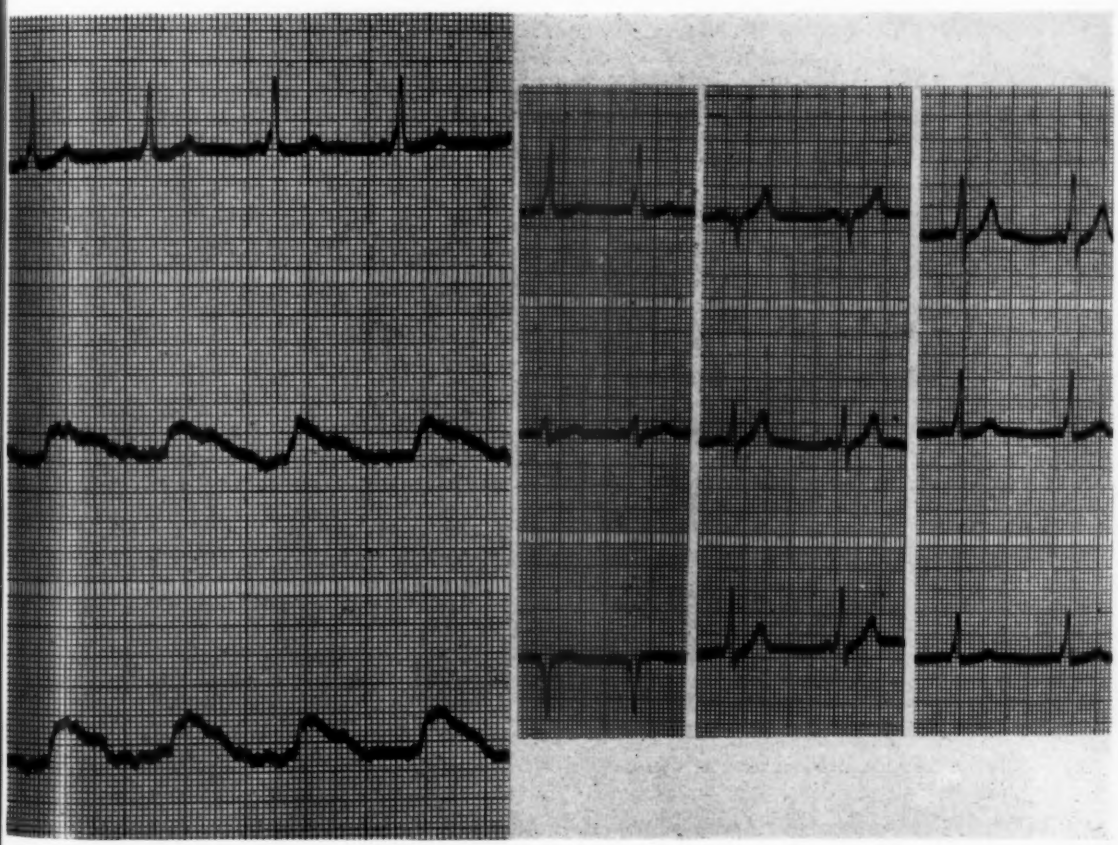
A. B.

Fig. 5.—W. B., Group B.

A, The electrokymogram: Lead II, ascending aorta and pulmonary artery from above down. The latter is 0.03 second ahead of the former. The relation is within normal limits.

B, The electrocardiogram: To the left are Leads I, II, and III from above down. The middle section shows Leads V_1, V_2, and V_3 from above down. To the right are Leads V_4, V_5, and V_6 from above down.

A possible explanation for the absence of mechanical asynchronism in most cases has been raised by Ferrer with the thought that "the location of the distal end of the aberrent pathway is sufficiently variable in patients with the bundle of Kent on the same side to account for entirely different sites of origin of the initial ventricular excitation as well as different sequences of depolarization." If the bundle of Kent ends near the ventricular septum, the depolarization wave would spread nearly simultaneously in the two ventricles and mechanical asynchronism would not be expected. If the bundle ends in one ventricle only, the pathway taken by the excitation wave to the other ventricle would be circuitous and result in prolonged ejection times and mechanical asynchronism. Prolonged ejection time on the side of the bundle would be explained by slow depolarization of the ventricle along muscular pathways instead of along the Purkinje system,



A B

Fig. 6.—C. S., Group B.

A, The electrokymogram: Lead I, ascending aorta and pulmonary artery from above down. The relation is minus 0.04, outside the normal range but in a direction opposite to that expected if correlation between the electrical and mechanical events occurred, since the electrocardiogram suggests a right bundle of Kent.

B, The electrocardiogram: To the left are Leads I, II, and III. The middle section shows Leads V_1, V_2, and V_4 from above down. The curve to the right shows Leads V_3, V_5, and V_6 from above down.

and if the depolarization wave were slow enough, could so delay ventricular contraction and ejection so as to reduce or obliterate mechanical asynchronism. This explanation assumes that there is a great deal of correlation between delay in electrical activation and delay in mechanical activation, and we question that assumption on the basis of our experience with mechanical and electrical asynchronism in the ninety-nine cases mentioned above.

There is still one further point we would like to mention. Grishman and Steinberg[42] have recently completed a study on Wolff-Parkinson-White syndrome using simultaneously recorded intracardiac (right auricle and right ventricle), esophageal, and precordial leads and, by a study of the delta wave[43] (the initial slurred portion of the QRS complex in the Wolff-Parkinson-White syndrome), have concluded that there are at least two bundles of Kent in each case of this syndrome. This is based on the finding that the delta wave first appears simultaneously as a negative wave over the anterior surface of the right ventricle (and as a positive wave in the right ventricular cavity, suggesting that depolarization proceeds from epicardium to endocardium instead of the reverse, as is normally the situation) and as a negative wave over the posterior part of the left ventricle as recorded in esophageal leads. At the same time the delta wave appeared as a positive wave over the left precordial leads. This suggests the presence of two bundles of Kent, one between the right auricle and ventricle, and one between the left auricle and ventricle. The presence of this abnormal bilateral conducting system, carrying an excitation wave simultaneously to the anterior surface of the right ventricle and the posterior surface of the left ventricle more slowly than excitation is carried by the bundle of His and the Purkinje fibers, would explain our finding of delayed mechanical ejection from both sides of the heart and the usual absence of ventricular mechanical asynchronism.

SUMMARY

In a study of fifteen cases of Wolff-Parkinson-White syndrome by simultaneously recording the electrokymograms of the ascending aorta and pulmonary artery together with an electrocardiogram in the right anterior oblique position, we have found mechanical asynchronism in only five cases but have found evidence of delay in ejection from both ventricles, regardless of the side of the bundle of Kent, in most instances.

We would like to express our gratitude to Dr. Arthur C. DeGraff, Senior Consultant to the Medical Service, Bronx Veterans Hospital, for the aid and encouragement which made the work possible.

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PROMINENT R WAVE AND SHALLOW S WAVE IN LEAD V_1 AS A RESULT OF LATERAL MYOCARDIAL INFARCTION

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DURING a recent study of electrocardiographic patterns in myocardial infarction[1] we observed a group of cases in which significant QRS changes were noted in the precordial Lead V_1. These consisted of an increase in amplitude of the R wave and decrease in amplitude of the S wave due to the absence of normal electromotive forces in the opposing left ventricular walls. It is the purpose of this communication to present twelve cases demonstrating such a pattern and to discuss its genesis.

The sequence of normal ventricular activation has been depicted by Gardberg and Ashman.[2] Four stages of ventricular activation may be utilized to describe the sequence of electrical activity which results in the QRS configuration usually obtained in Lead V_1 in adults. In the first stage, a small initial R wave results from septal activation which causes positivity at the precordial electrode. This is probably due to a greater initial area of activation on the left side of the septum. In the second stage, depolarization of the septum progresses, and the wave front extends to involve the adjacent left and right ventricular walls and to break through the epicardial area of the apical region of the right ventricle, resulting in beginning negativity at the precordial site. In the third stage, right ventricular activation has proceeded almost to completion, and maximal negativity results as the wave of excitation is spreading through the free and basilar walls of the left ventricle, the apical region of the left ventricle having become depolarized. The fourth stage results in decreased negativity due to shrinking of the shell of activation which is extending through the high lateral and basal walls of the left ventricle. The effects of activation in the pulmonary conus area have been neglected in the above discussion. A clear three-dimensional picture of electrical activation may be secured by referring to the paper by Gardberg and Ashman.[2]

The QRS changes produced by infarction as observed in our cases affect mainly stages two and three. The QRS configuration in Lead V_1 is a resultant of electrical activity in opposing right and left ventricular walls, the septum not significantly affecting the potential in these stages. The process of infarction results in a disappearance of the deep S wave which normally appears and its replacement by a large R wave. This is due to absence of normal opposing electromotive forces in the left ventricle. The right and left ventricular areas

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Received for publication March 11, 1950.

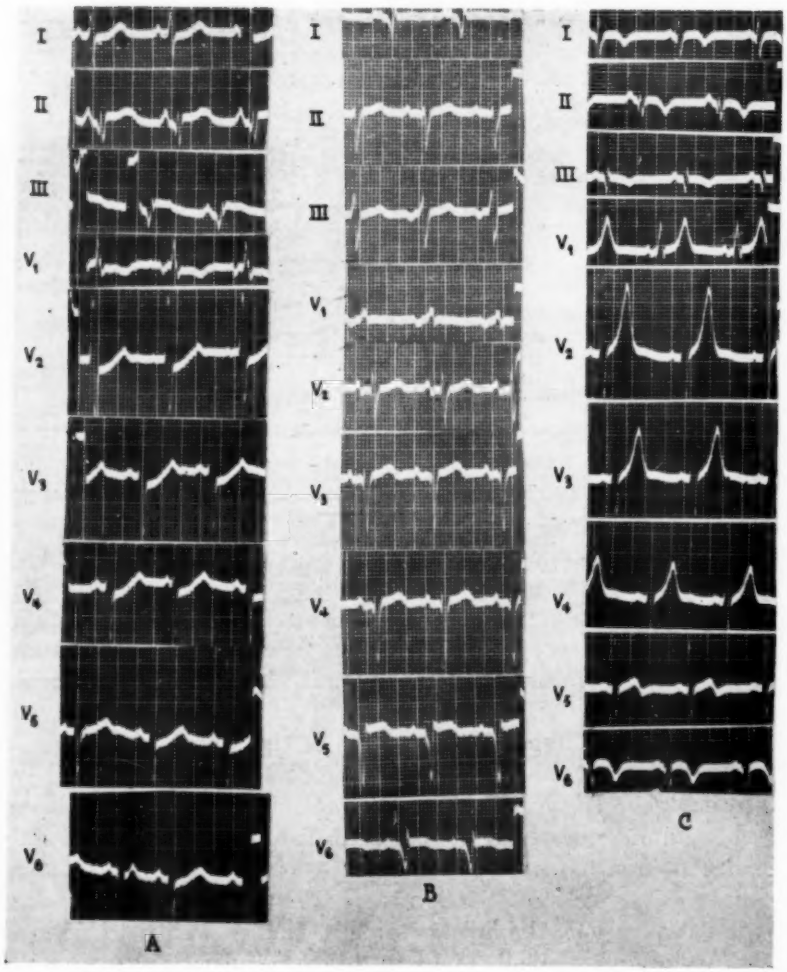

Fig. 1.—*A*, Case 1. There is a recent posterior myocardial infarction with prominent $Q_{2,3}$ and a high R wave in V_1 followed by a small S wave in V_1.

B, Case 2. There is a recent anterolateral myocardial infarction with Q_1 and $V_{2,4,5,6}$ and a prominent R wave in V_1 followed by a very small S wave in V_1.

C, Case 3. There is a posterolateral myocardial infarction with $Q_{2,3}$ and V_6 and a high R wave in V_1 followed by a small S wave in V_1.

whose electromotive forces play a predominant role in the production of the QRS configuration in Lead V_1 will depend on the degree of rotation of the heart on its anteroposterior, longitudinal, and transverse axes.[2] Unless previous tracings have been made, once infarction has occurred the degree of rotation about the three axes is difficult to estimate from the electrocardiogram.

The electrocardiograms of Figs. 1 to 4 were recorded from patients who presented clinical pictures characteristic of myocardial infarction. The standard limb leads and Leads V_1 through V_6 were recorded in all cases. A prominent

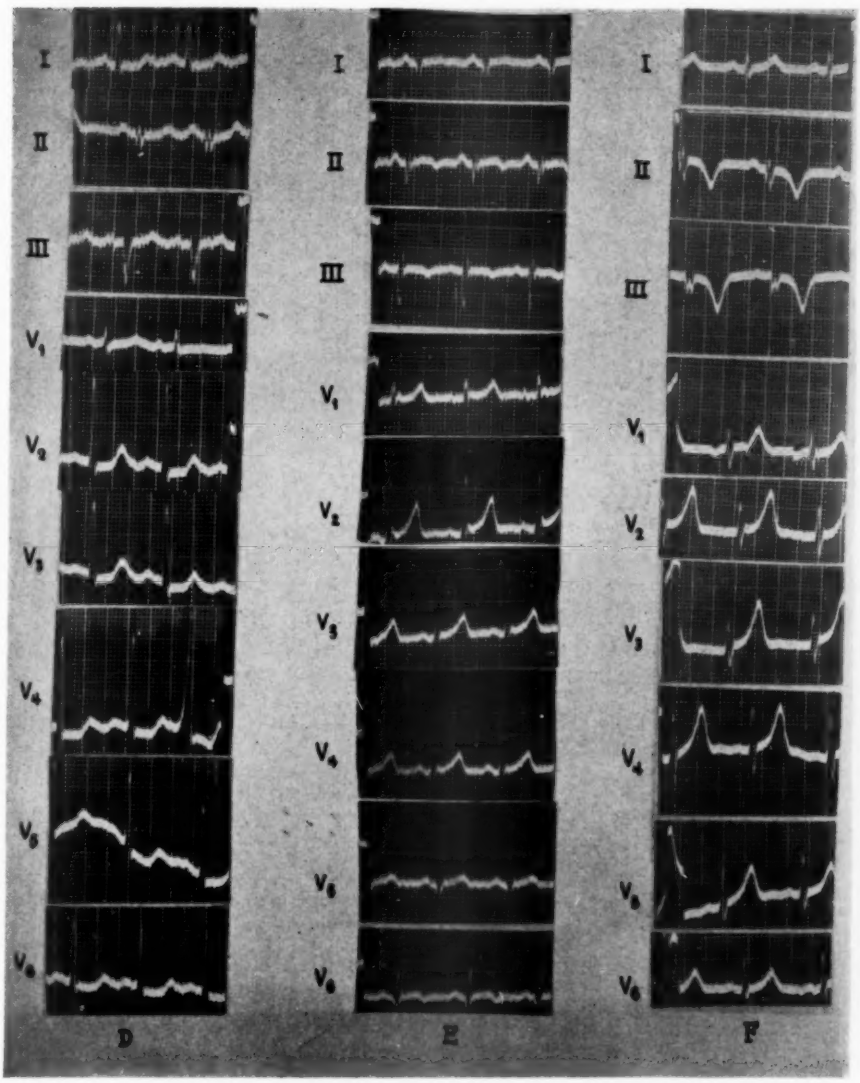

Fig. 2.—*D*, Case 4. There is a healed posterior myocardial infarction with $Q_{2,3}$ and a prominent R wave in V_1.

E, Case 5. There is a recent posterolateral myocardial infarction with $Q_{1,2,3}$ and $V_{5,6}$ and a prominent R wave in V_1.

F, Case 6. There is a posterior myocardial infarction with $Q_{2,3}$ and a prominent R wave in V_1.

R wave in V_1 occurred as a result of myocardial infarction localized electrocardiographically in the posterior wall in three cases (1, 4, 6), in the posterolateral wall in eight cases (3, 5, 7-12), and in the anterolateral wall in one case (2). In Cases 8 and 12 there was also a prominent R wave in Lead VR; this was due to the absence of opposing electrical effects in the posterolateral infarcted wall.

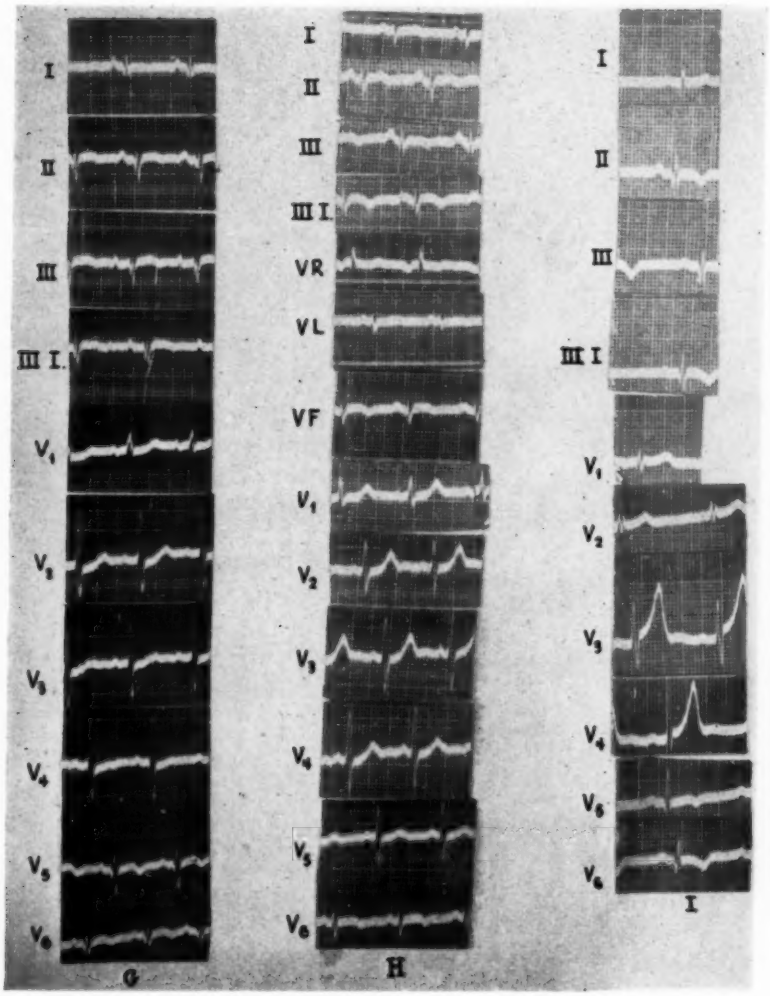

Fig. 3.—III_1 = Lead III with deep inspiration.

G, Case 7. There is a posterolateral myocardial infarction with $Q_{1,2,3}$ and $V_{5,6}$ and a high R wave in V_1.

H, Case 8. There is a posterior infarction with probable lateral involvement. There is $Q_{2,3}$, VF and a small R_1 and V_6 with a prominent R wave in VR and in V_1.

I, Case 9. There is a posterolateral myocardial infarction with $Q_{2,3}$ and $V_{5,6}$ and prominent R wave in V_1.

DISCUSSION

Although the variation in cardiac rotation accounts for the fact that the potential from slightly different ventricular areas exerts a prominent effect at precordial position 1, the area of the left ventricle which yields the major portion of the opposing electromotive forces consists of the lateral wall. In clockwise-rotated hearts the anterolateral wall will yield the major opposing forces; in

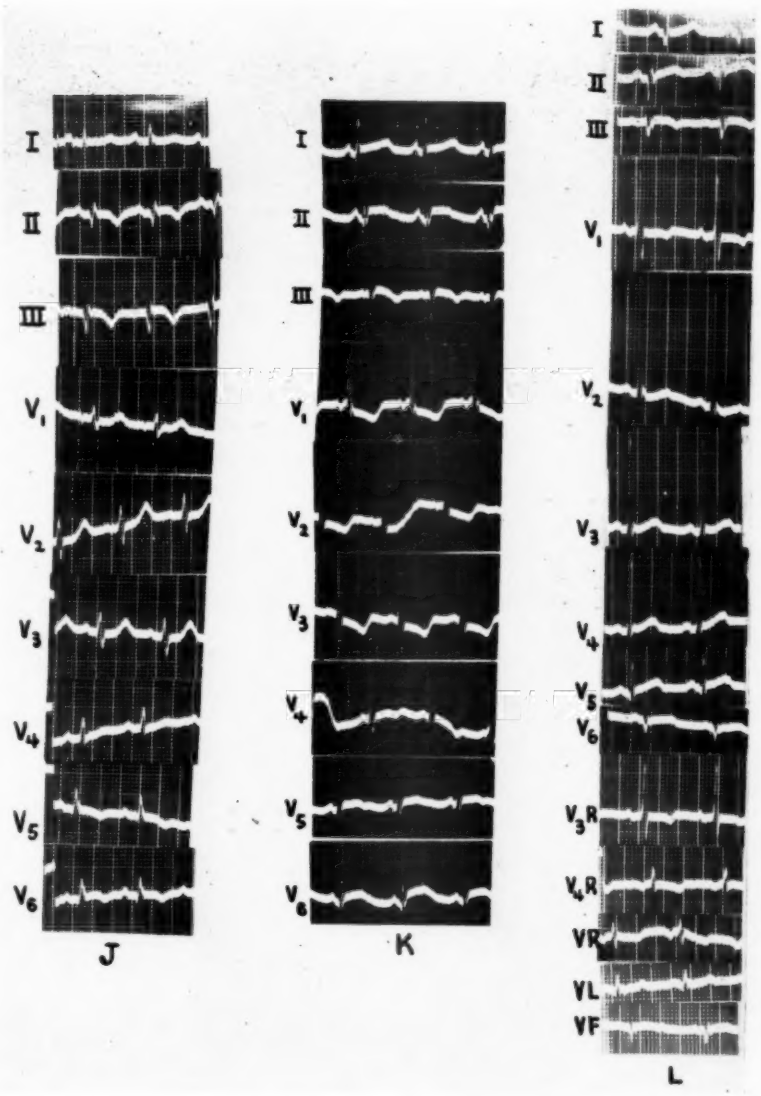

Fig. 4.—*J*, Case 10. There is a posterolateral myocardial infarction with $Q_{2,3}$ and $V_{5,6}$ and prominent R wave in V_1.

K, Case 11. There is a posterolateral myocardial infarction with $Q_{2,3}$ and V_6 and a high R wave in V_1.

L, Case 12. There is a posterolateral myocardial infarction with $Q_{2,3}$ and V_6, VF and a prominent R wave in V_1, V_R, V_3R, V_4R. V_3R is taken at the fifth intercostal space in the right midclavicular line and V_4R is taken at the fifth intercostal space in the anterior axillary line.

counterclockwise-rotated hearts the posterolateral wall will contribute the predominating opposing forces. Strictly posterior or posteroseptal infarction usually does not result in a high V_1 since electromotive forces produced in this area are directed mainly perpendicular to the frontal plane.

Just as one finds high T waves frequently recorded from precordial positions 1, 2, and 3 when posterior ischemia with inverted $T_{2,3}$ is present and depression of RS-T segments in the precordial leads seen opposite posterior injury, one may therefore expect at times to find QRS changes when leads are taken at chest areas where the predominant electromotive forces are directly opposed to those of the infarcted region.

SUMMARY

Twelve cases are presented with electrocardiograms showing a prominent R wave and decrease in amplitude of the S wave in Lead V_1 due to myocardial infarction disturbing the normal opposing electromotive forces which cause a deep S wave in Lead V_1.

We wish to thank Dr. Richard Ashman for his suggestions which prompted the investigation of this subject and the consequent completion of this paper.

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THE ELECTROCARDIOGRAPHIC DIAGNOSIS OF COMBINED LEFT AND RIGHT VENTRICULAR STRAIN

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THE electrocardiographic pattern of unilateral ventricular strain has been extensively studied during the past two decades by many investigators. More recently, the importance of the "electrical" position of the heart and its effect on electrocardiographic patterns have been stressed by Wilson and his associates.[1] The effect of various "electrical" positions on patterns of heart strain has been well delineated with the aid of the V and augmented V (aV) limb leads. These studies have been limited to the consideration of either left[1-3] or right[1,4,5] ventricular strain. However, a survey of the literature has revealed a marked paucity of information concerning electrocardiographic patterns of combined left and right ventricular strain. Previous studies of this subject from this department[6-9] were limited in scope because fewer electrocardiographic leads were then commonly employed. On this account it was felt desirable to re-evaluate the problem of combined ventricular strain with the aid of multiple limb and precordial leads.

SUBJECTS STUDIED AND METHODS EMPLOYED

Rheumatic heart disease, by virtue of its frequent multiple valvular involvement, often gives rise dynamically to combined left and right ventricular enlargement. For this reason, the electrocardiograms of fifty patients with chronic rheumatic heart disease were selected from 515 records obtained during a previous study[10] for evidence of combined ventricular strain. As a result of certain combinations seen in the electrocardiograms of these rheumatic patients associated with left ventricular strain and suggesting the presence of combined ventricular strain, it was felt desirable to study left ventricular strain patterns in nonrheumatic patients for comparison. For this purpose, an additional eighty-five patients with heart disease, nonrheumatic in origin, and a left ventricular strain pattern were also reviewed. Electrocardiograms showing evidence of myocardial infarction, acute cor pulmonale, or digitalis effect were not included because such records are known to imitate right, left, or combined ventricular strain.[6]

In these 135 patients, the electrocardiograms consisted of Leads I, II, III, aV_R, aV_L, aV_F, V_1 to V_7, V_{3R} and V_{4R} in each instance. V chest leads were obtained with the use of the central terminal of Wilson and associates.[11] The aV

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Received for publication April 6, 1950.

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TABLE I. CORRELATION OF DATA IN 32 RHEUMATIC PATIENTS WITH ELECTROCARDIOGRAPHIC PATTERNS OF VENTRICULAR STRAIN

VENTRICULAR ENLARGEMENT (ANATOMIC)	VENTRICULAR STRAIN PATTERN (ECG)	NO. CASES	"ELECTRICAL" POSITION*					CLOCK-WISE ROTATION	INCIDENCE OF		CLINICAL DIAGNOSIS		
			H.	S.H.	I.	S.V.	V.		P-MITRALE	AU-RICULAR FIBRILLA-TION	MITRAL INSUFFI-CIENCY	MITRAL INSUFFI-CIENCY AND STENOSIS	MITRAL AND AORTIC LESIONS
Combined right and left ventricle	Combined	8		1			7	7	4	3		3	5
	Left	11			6	3	2	4	2	5		6	5
	Right	2		1			1	2		1		2	
Left	Left	6		2		3	1	2		1	3		3
Right	Combined	1					1	1		1		1	
	Left	1					1						1
None	Left	2					2		1		1	1	
	Right	1					1	1				1	

* H. = horizontal
S.H. = semihorizontal
I. = intermediate
S.V. = semivertical
V. = vertical

limb leads were obtained by the method of Goldberger[12] modified by the introduction of a 5,000 ohm resistance in every connection of the indifferent electrode to minimize current flowing through the skin.[13] The amplitudes of R, S, and T waves, the R/S and R/T ratios, and the ventricular activation time (time of onset of the "intrinsicoid" deflection) of right-sided and left-sided precordial leads were measured, and the patterns in the aV limb leads were carefully analyzed. These values and patterns were then subjected to comparison with those described for isolated left[3] or right[5] ventricular strain, and the exceptions noted. The criteria employed for the electrocardiographic diagnosis of left or right ventricular strain in the V chest and the aV limb leads were those recently set forth by Sokolow and Lyon.[3,5]

Determination of anatomic enlargement of the ventricles was based on fluoroscopic examination, supplemented by roentgen films in many instances and by post-mortem observations in two patients whose electrocardiograms were indicative of combined ventricular strain.

Throughout the following discussion the term ventricular enlargement refers to anatomic enlargement; the term ventricular strain refers to electrocardiographic evidence of ventricular strain. The expression, clockwise rotation, refers to a shift of the transition zone to the left of Lead V_4 in the serial precordial leads. In the following discussion, and in Table I, only those valvular lesions are listed for which there was evidence of their dynamic importance. The patients, chosen at random, were of various ages and included children.

RESULTS

Of the fifty patients with rheumatic heart disease, the electrocardiograms were normal in eleven instances and showed nonspecific abnormalities in seven others. There was no evidence of heart strain in these records, despite the presence of dynamically important valvular lesions and cardiac enlargement in thirteen of these eighteen patients.

The remaining thirty-two electrocardiograms indicated various types of ventricular strain (Table I). Enlargement of both ventricles was present in twenty-one patients (66 per cent). Dynamic mitral stenosis and insufficiency, with or without dynamic aortic insufficiency, were present in the twenty-one patients; their electrocardiograms demonstrated a pattern of right ventricular strain in two cases, left ventricular strain in eleven, and combined ventricular strain in eight instances (Figs. 1 and 2). The diagnosis of combined ventricular strain was based upon evidence in the precordial leads, some of which pointed to left, and some to right, ventricular strain. Left ventricular strain was indicated by tall R waves, S-T depressions, and/or T-wave inversion in the left-sided precordial leads; right ventricular strain was indicated by tall, and usually late, R waves, S-T depressions, and deep T inversion in leads V_{4R} to V_2. Various combinations of these abnormalities were present concomitantly, depending primarily on whether left or right ventricular strain was predominant. In addition, P-mitrale or auricular fibrillation, a vertical "electrical" position, and clockwise rotation on the longitudinal axis were present in all but one of the electrocardiograms demonstrating combined ventricular strain, and were present in the electrocardiograms of five of the thirteen patients which demonstrated

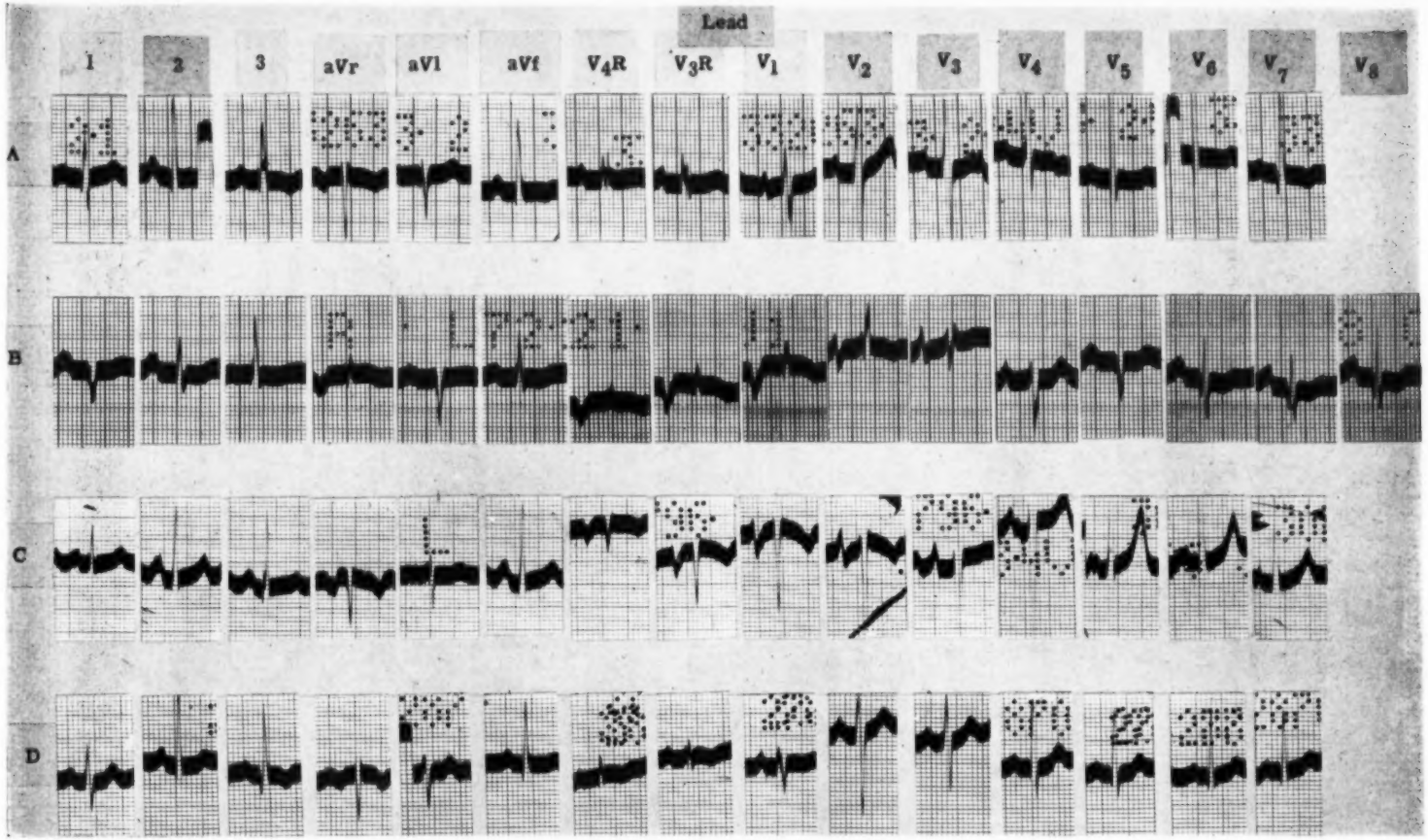


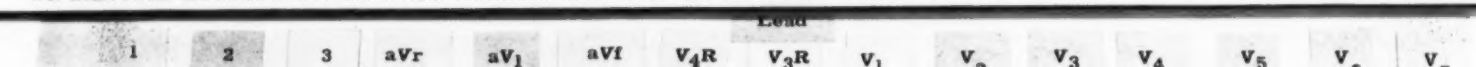
Fig. 1.—Four electrocardiograms demonstrating combined ventricular strain.

Case A was obtained from a 12-year-old girl with an aortopulmonary septal defect, left ventricular enlargement, and pulmonary hypertension (38/22 mm. Hg pressure in pulmonary artery and 65/5 mm. Hg in right ventricle). Electrocardiogram reveals left ventricular strain (Leads aV_F, V_6, V_7) and a delayed "intrinsicoid" deflection related to the right heart strain (Leads V_{4R}, V_{3R}).

Case B was obtained from a 15-year-old girl with aortic and mitral lesions and combined ventricular enlargement. The pattern of right ventricular strain can be seen in most leads. Concomitant left ventricular strain is indicated by T-wave inversion in the left-sided chest (Leads V_6 to V_8).

Case C was obtained from a 38-year-old woman with aortic and mitral lesions and combined ventricular enlargement. The deep S wave in Leads V_2 and V_3 and the tall R wave in V_6 are manifestations of left ventricular strain[3] and the deep T inversions in Leads V_{3R} and V_1 are believed to be representative of the right ventricular strain.

Case D was obtained from a 14-year-old girl with mitral stenosis and insufficiency and combined ventricular enlargement. Abnormalities indicative of left heart strain are noted in aV_F and of right ventricular strain in the tall, late R wave in Leads V_{3R} to V_1.



V_3 and the tall R wave in V_6 are manifestations of left ventricular strain and the deep T inversions in Leads V_{3R} and V_1 are believed to be representative of the right ventricular strain.

Case D was obtained from a 14-year-old girl with mitral stenosis and insufficiency and combined ventricular enlargement. Abnormalities indicative of left heart strain are noted in aV_F and of right ventricular strain in the tall, late R wave in Leads V_{4R} to V_1.

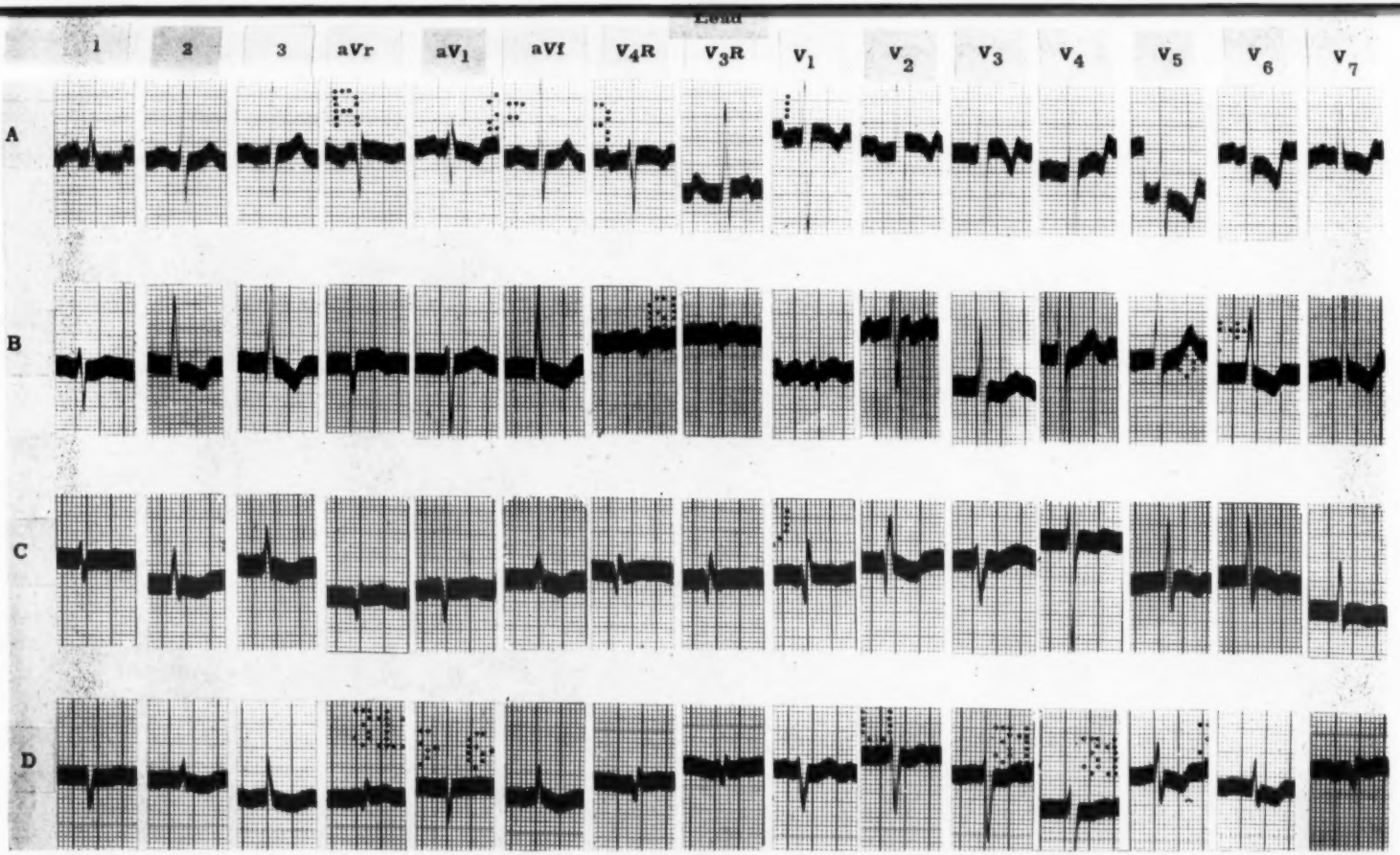


Fig. 2.—Four electrocardiograms demonstrating combined ventricular strain.

Case A was obtained from a 12-year-old girl with mitral stenosis and insufficiency and combined ventricular enlargement. Left ventricular strain is revealed in the left-sided chest leads; the tall R wave in V_{3R} and T-wave inversion in Leads V_{4R} to V_1 are believed to be indicative of right ventricular enlargement.

Case B was obtained from a 35-year-old woman with mitral stenosis and insufficiency and enlargement of both ventricles (proved at necropsy). A characteristic left ventricular strain can be seen in aV_F, V_6, and V_7. The tall R wave and T inversion in V_2 and the small complex in V_1 are associated with the right heart strain. (A similar pattern was observed in another patient with similar clinical manifestations.)

Case C was obtained from a 50-year-old man with aortic, mitral, and tricuspid valve lesions and marked biventricular enlargement without significant coronary sclerosis (proved at necropsy). Right heart strain is reflected in the right chest leads which may indicate a minor conduction defect. The T-wave inversions in V_6, V_7, and aV_F reflect the left ventricular strain.

Case D was obtained from a 63-year-old woman with mitral stenosis and insufficiency and combined enlargement. Right heart strain is reflected in the tall, late R waves in V_{4R}, V_{3R}, and aV_R. The T-wave inversion in Leads V_5 and V_6 is probably indicative of the concomitant left ventricular strain.

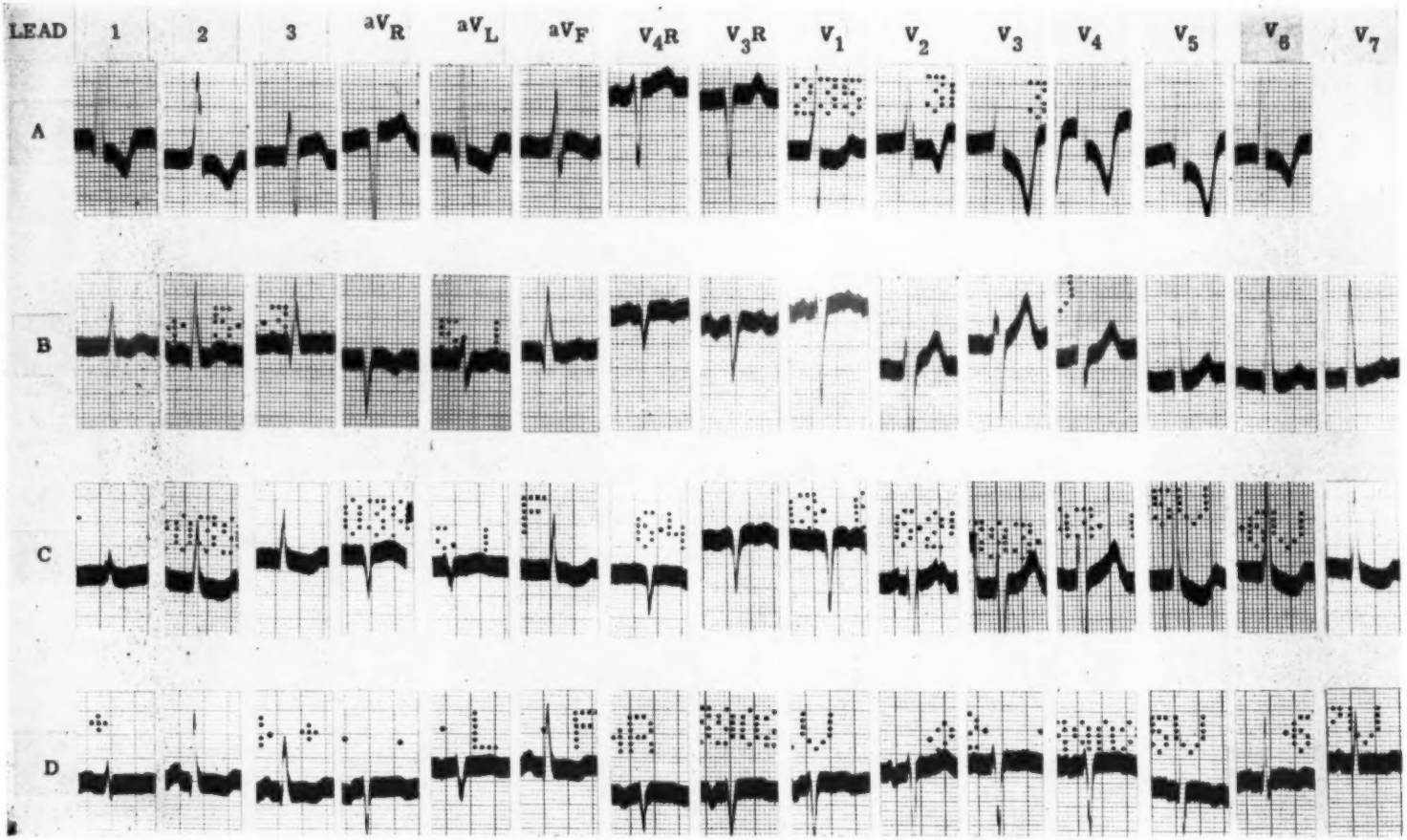


Fig. 3.—Case A was obtained from a 70-year-old man with hypertension and advanced left ventricular strain, seimhorizontal position with marked counterclockwise rotation (Compare with Fig. 2, Case A).

Cases B and C were obtained from a 43-year-old man and a 30-year-old woman with mitral stenosis and insufficiency and combined ventricular enlargement. The electrocardiograms indicate left ventricular strain; a vertical position, clockwise rotation, and auricular fibrillation reflect concomitant right ventricular strain.

Case D was obtained from a 70-year-old man with hypertension, left ventricular hypertrophy, and marked emphysema (proved at necropsy). The electrocardiogram indicates left ventricular strain. The vertical position and clockwise rotation were affected by the marked emphysema.

only isolated left or right ventricular strain. Furthermore, the tetrad—an "electrical" position other than horizontal or semihorizontal, clockwise rotation, auricular fibrillation or P-mitrale and left ventricular strain—was present only in patients with combined ventricular enlargement.

Isolated left ventricular enlargement was present in six cases; the electrocardiograms of each indicated isolated left ventricular strain. Isolated right ventricular enlargement was present in two cases; the electrocardiogram in one of these demonstrated combined ventricular strain and, again, was associated with a vertical position, auricular fibrillation, and clockwise rotation. A pattern of isolated left ventricular strain was present in two cases and of isolated right ventricular strain in one case with fluoroscopically normal heart sizes. A vertical position was often present and auricular fibrillation and clockwise rotation occurred occasionally in these patients. However, the triad of these features was present only in the record with combined strain.

The second group of eighty-five patients with an electrocardiographic picture of left ventricular strain had the following diagnoses: twenty, arteriosclerotic heart disease; forty-eight, hypertensive heart disease; eight, syphilitic heart disease (with dynamic aortic insufficiency); four, congenital heart disease; one, myxedema; one, anemia; and three, diagnosis not established. On fluoroscopic examination, six patients had a normal heart size, seventy-seven had isolated left ventricular enlargement, and two had both left and right ventricular enlargement. The "electrical" position was horizontal in thirty instances, semihorizontal in eight, intermediate in twenty, semivertical in eleven, and vertical in sixteen. Sinus rhythm was present in all but one case, the latter having auricular fibrillation. Moderate to marked clockwise rotation was observed in sixteen electrocardiograms, of which eleven were in a vertical and semivertical position. Various factors were present in these cases which contributed toward effecting an "electrically" vertical heart with or without clockwise rotation; e.g., certain patients were in the younger age group, and emphysema was present in many of the older ones (Fig. 3, Case D). Furthermore, this "electrical" position was commonly noted in left ventricular strain associated with dynamic aortic insufficiency, probably due to the downward enlargement of the left ventricle.

The classical pattern of left heart strain in various "electrical" positions was observed in each instance. Only one electrocardiogram in this group of patients presented evidence to suggest concomitant right ventricular strain (Fig. 1, Case A), and an electrocardiogram recorded four months previously was entirely within normal limits. The pattern in V_{4R} and V_{3R} may represent a focal block in the free wall of the right ventricle,[16] in all probability related to the right ventricular strain since an electrocardiogram obtained four months before was normal.

The age of the patients in this study did not influence the pattern of combined strain.

DISCUSSION

Information concerning electrocardiographic patterns indicative of combined left and right ventricular strain is scattered. This is probably accounted for by

trocardiogram indicates left ventricular strain. The vertical position and clockwise rotation were affected by the marked emphysema.

the infrequent appearance of electrocardiograms actually demonstrating such abnormalities. Various studies have suggested an apparent domination of the normal electrocardiogram by the activation of the left ventricle over that of the thinner-walled right ventricle.[14] Such left-sided domination is proportionately magnified in cases with left ventricular enlargement. This magnified left ventricular domination usually overshadows the increased influence of a concomitantly enlarged right ventricle. However, in the presence of isolated right ventricular enlargement, the influence of the right ventricle will ordinarily exceed that of the normal left ventricle, and a pattern of right ventricular strain will be inscribed in the electrocardiogram. Marked right ventricular enlargement, for similar reasons, produces an electrocardiographic pattern of right ventricular strain when the associated left ventricular enlargement is relatively slight in degree. Thus, an electrocardiographic pattern of left or right ventricular strain may represent either unilateral or preponderant enlargement of the respective ventricle.[9] This fact explains why in electrocardiographic practice isolated left or right ventricular strain patterns are usually encountered.

In the presence of combined ventricular enlargement, the influence of each ventricle may "neutralize" the other, thereby producing an electrocardiogram approaching normality or with nonspecific abnormalities.[15] Thus, anatomical correlative studies and our own data have not infrequently shown an absence of axis shift or evidence of ventricular strain in the presence of bilateral ventricular enlargement.[6] Diagnostic evidence of both left and right ventricular enlargement, for these reasons, will be observed in the same electrocardiogram only infrequently.

The classical limb lead pattern of left ventricular strain[16] is that usually observed in "electrically" horizontal or semihorizontal positions. Kaplan and Katz,[17] in describing the so-called concordant pattern of left heart strain, proposed that the absence of axis shift in the ordinary limb leads might be due to concomitant right ventricular enlargement. This suggestion became substantiated with the realization that right ventricular enlargement was commonly observed at necropsy in patients with chronic left ventricular strain.[18] Later, certain limb lead patterns,[6] occasionally in combination with certain precordial lead patterns,[7] were interpreted as evidence of combined heart strain; these correlated well with anatomic enlargement of both ventricles.[6-9] The more recent realization of the effect of the "electrical" position on the limb lead pattern has considerably clarified this problem. It is now recognized that a concordant upright or inverted pattern or an axis shift to the right in the limb leads in association with a precordial pattern of left ventricular strain represents patterns of left heart strain in various "electrical" positions.[1,19] It is now clear that such records present electrocardiographic evidence only of left ventricular strain.

Nevertheless, it was apparent from previous anatomic correlations[6] that patterns of left ventricular strain in "electrical" positions other than the horizontal were frequently encountered in patients with bilateral ventricular enlargement. It was further reasoned that in certain instances of left ventricular strain the less commonly observed "electrical" positions might be due to positional changes caused by a concomitant right ventricular enlargement. This becomes more

plausible with the realization that the pattern of left ventricular strain is predominant in electrocardiograms of rheumatic subjects, even in those with multiple valvular involvements.[20,21] We have attempted in this study to find features which might distinguish the latter electrocardiograms from instances in which the "electrical" position was due to other factors, such as emphysema[22] or downward enlargement of the left ventricle as in marked aortic insufficiency.

Diagnostic electrocardiographic evidence of combined ventricular strain was observed in nine out of twenty-one records from rheumatic patients with combined ventricular enlargement. There was a marked cardiomegaly in all but one patient whose electrocardiograms revealed combined ventricular strain. In an electrocardiogram revealing primarily left ventricular strain, criteria of concomitant right ventricular strain include changes similar to those seen in records with isolated right ventricular strain. The latter changes would be expected particularly in right-sided precordial leads in closest proximity to the right ventricle. In other words, in records primarily indicative of left ventricular strain, the changes due to concomitant right heart strain are observed in leads V_{4R}, V_{3R}, V_1, and V_2; they include tall R waves, suggestive evidence of delayed right ventricular activation, S-T depressions, and T-wave inversions. Deep S waves in left-sided chest leads may be corroborative evidence of concomitant right heart strain. T inversions to be significant should be marked, probably should occur in several right-sided chest leads, and should be associated with a well-delineated pattern of left ventricular strain in other leads. Examples of tall R waves in Leads V_1, V_{3R}, and V_{4R} are shown in Fig. 1, Case D and Fig. 2, Case A; examples of T-wave inversions in these leads are shown in Fig. 1, Case C, and Fig. 2, Cases A and B; a late "intrinsicoid" deflection is illustrated in Fig. 1, Case A and Fig. 2, Cases C and D.

The use of these criteria for the diagnosis of combined ventricular strain should be applied carefully. The presence of tall R waves, S-T depressions, and T-wave inversion in right-sided precordial leads may not always represent activation of the right ventricle and, therefore, need not indicate right ventricular strain. Such alterations must be carefully distinguished from tall R waves and T inversions in these leads which represent left ventricular activity. Fig. 3, Case A, illustrates such a record in which the tall R waves and S-T-T changes in Leads V_1 and V_2 are derived from the activation of the free wall of the left ventricle and appear in these leads because of obvious marked counterclockwise rotation. The record reveals a pattern of advanced left ventricular strain with a marked shift of the transition zone to the right side of the serial precordial electrocardiogram. Moreover, in an electrocardiogram indicative of left ventricular strain, the presence of deep S waves in left-sided precordial leads alone cannot be used as a definite criterion of concomitant right ventricular strain; such deflections may result entirely from clockwise rotation.

Sokolow and Lyon[3] have called attention to the importance of R/S and R/T ratios and have set up inclusive values for them in Leads V_1 and V_2 in electrocardiograms revealing left ventricular strain. It is apparent that a taller R wave or a T-wave inversion in these leads will significantly alter these ratios, as is illustrated in Fig. 1, Case D, and Fig. 2, Case B. It has been our experience that

such deviations from their values should be used with caution as criteria of combined strain and may be useful only in records where there is a pattern of advanced left ventricular strain in Leads V_5 and V_6.

In electrocardiograms primarily indicative of right ventricular strain, evidence of concomitant left ventricular strain was manifested, in our experience, by T-wave inversion in left-sided chest leads (Fig. 1, Case B), when other causes for the latter inversion could be excluded.

A definite diagnosis of combined ventricular strain must rest on findings such as those described above and as illustrated in Figs. 1 and 2. It was noted that certain other features were present in many of the cases demonstrating combined strain, including an "electrically" vertical position, clockwise rotation, and auricular fibrillation or P-mitrale. This triad was present in four of the cases, two of the three features were seen in three cases, and one of these features was found in two cases in the rheumatic group. Eleven other electrocardiograms from rheumatic patients with biventricular enlargement revealed only left ventricular strain, and two revealed only right ventricular strain. An "electrically" vertical, semivertical, or intermediate position, clockwise rotation, and auricular fibrillation or P-mitrale were also present in many of the latter records. Fig. 3, Cases B and C, illustrate electrocardiograms of this type. In this study auricular fibrillation and P-wave abnormalities in records with left heart strain were present, with two exceptions, only in patients with combined ventricular enlargement. Nevertheless, it is known to occur in mitral stenosis in the absence of ventricular enlargement. Furthermore, "electrical" verticality and clockwise rotation were occasionally present in instances without combined ventricular enlargement. Thus, none of the triad of features alone provides absolute criteria for the diagnosis of combined ventricular strain when associated with a pattern of left ventricular strain. However, the presence of these criteria, particularly auricular fibrillation and clockwise rotation in rheumatic patients, is presumptive evidence of additional right ventricular strain in an electrocardiogram actually demonstrating only left ventricular strain. The entire triad of features, in association with a pattern of left ventricular strain, was encountered only in patients with combined ventricular enlargement. That such a pattern usually occurs only in patients with biventricular enlargement and, therefore, can be interpreted as indicating combined ventricular strain, is well supported by previous[6-9] and more recent[23,24] anatomic correlations. It is perhaps of added significance that in the other rheumatic patients whose electrocardiograms revealed left heart strain, despite an absence of apparent combined ventricular enlargement, every instance of clockwise rotation and "electrically" vertical position occurred in patients with dynamic mitral stenosis and insufficiency, and in some a dynamic aortic lesion was also present. The same criteria have not been found applicable to nonrheumatic patients in this study (see Fig. 3, Case D). In the nonrheumatic patients, the vertical or semivertical position, with or without clockwise rotation, was often affected by emphysema,[22] younger ages, or aortic insufficiency with downward enlargement of the left ventricle.[1] Furthermore, auricular fibrillation occurs in arteriosclerotic heart disease. Some of the limb lead patterns previously associated with biventricular enlargement[6] were not encountered in this study and remain to be evaluated.

While this study was in progress, another dealing with this problem appeared in the French literature.[23] These authors have arrived at conclusions closely paralleling ours. They cited instances of combined ventricular strain with patterns and criteria similar to those seen by us. It is further significant that anatomic correlations in rheumatic patients revealed that electrocardiograms showing left ventricular strain in positions other than the horizontal, particularly when associated with a clockwise rotation, were usually found in patients with combined ventricular hypertrophy. In another recent study[24] it was found that the commonest pattern in rheumatic patients with biventricular enlargement, usually secondary to combined mitral and aortic valve lesions, was that of left ventricular strain in a vertical position and with clockwise rotation. Despite the similarity of these conclusions it should again be emphasized that previous anatomic correlations,[6,17] as well as the present study, have shown that electrocardiograms revealing left ventricular strain in other than a horizontal position will not infrequently be found in instances of isolated left ventricular enlargement in rheumatic and particularly in nonrheumatic patients. Further anatomic correlative studies would be desirable in this regard.

SUMMARY

Evidence of combined left and right ventricular strain has been sought in electrocardiograms obtained from fifty patients with rheumatic heart disease. The data have been correlated with clinical, fluoroscopic, and, in a few instances, post-mortem findings. Standard and aV limb and precordial leads V_1 to V_7, V_{3R} and V_{4R} were recorded in each instance.

In two electrocardiograms primarily revealing right ventricular strain, concomitant left ventricular strain was indicated by T-wave inversion in the left-sided precordial leads. In seven records primarily revealing left ventricular strain, evidence of concomitant right ventricular strain was indicated by tall and/or late R waves, S-T depressions, T-wave inversion, and a large R/S ratio in the right-sided precordial leads (V_{4R}, V_{3R}, V_1, and V_2). Certain other features were commonly present in these electrocardiograms, viz., a vertical "electrical" position, clockwise rotation (viewed from the apex), and auricular fibrillation or P-mitrale. Mitral stenosis and insufficiency and occasionally an associated aortic insufficiency were present in each instance. Combined ventricular enlargement was observed fluoroscopically or at necropsy in all but one patient in this group.

Electrocardiograms revealing only left ventricular strain when associated with an "electrical" position other than the horizontal or semihorizontal, and with a clockwise rotation and P-mitrale or auricular fibrillation were always obtained from patients with combined ventricular enlargement. The presence of only one or two of these features in conjunction with a pattern of left ventricular strain was frequently, but not invariably, found in patients with biventricular enlargement. The results of this study are in harmony with previous anatomic correlations from this department[6-9] and elsewhere.[23,24]

An additional eighty-five electrocardiograms of left heart strain obtained from nonrheumatic patients were analyzed for comparative purposes. In this

group of cases, a vertical or semivertical position and clockwise rotation were affected by emphysema, downward enlargement of the left ventricle in aortic insufficiency, or merely the vertical position usually observed in children. Evidence of concomitant right ventricular strain was observed in one record obtained from a patient with left ventricular enlargement and pulmonary hypertension secondary to an aortopulmonary septal defect.

CONCLUSIONS

1. Electrocardiograms that actually demonstrate combined ventricular strain are seen infrequently.

2. Electrocardiograms that inferentially demonstrate such patterns are observed more commonly. In patients with chronic rheumatic heart disease, a pattern of left ventricular strain associated with (a) an "electrical" position other than the horizontal or semihorizontal, (b) clockwise rotation, and (c) auricular fibrillation or P-mitrale may be interpreted as combined ventricular strain. The "electrical" position in such cases reflects the right ventricular enlargement. The presence of only one or two of this triad of features in conjunction with a pattern of left ventricular strain is frequently, but not invariably, found in patients with biventricular enlargement.

3. Similar criteria do not necessarily apply to nonrheumatic patients because other factors are operative more commonly.

We are indebted to the other members of the Department for their assistance in the conduct of this study.

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EXPLANATION OF THE WOLFF-PARKINSON-WHITE SYNDROME

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IN THE last year, by investigating the electrocardiograms of birds with modern methods, the following facts could be proved in all types of investigated birds (seagulls, chickens, pigeons, ducks): The subepicardial part of the heart is activated before the subendocardial part. This is proved by the fact that the intrinsic deflection of the QRS complex of the ventricle on most parts of the surface of the heart starts about 0.02 to 0.025 second earlier than in the right or left ventricular cavity. Accordingly, the mentioned groups of birds show as the main ventricular deflection on the surface of the heart in direct leads a deep negative deflection (S or QS), whereas if the exploring electrode is placed inside of each of the ventricles the ventricular complexes show as the main deflection a high upstroke (R or QR).[1]

Similar conditions were found for the heart of the calf in experiments performed together with F. M. Groedel and P. R. Borchardt,[2] and from previous literature it can be concluded that it may occur in a similar way in fully grown cattle and in horses. But for these animals no experimental data gained by modern investigations are available as yet.

It is an important fact that in every one of the mentioned types of animals a well-developed atrioventricular conductive system is present, and the only possible explanation is that the stimulus along the fibers of this system reaches the subepicardial heart muscle earlier than the subendocardial. The latter may be activated either directly via the heart muscle syncytium or with a physiologic delay via the conductive system.

After this condition has been proved as a fact for different groups of animals (calves, seagulls, chickens, pigeons, and ducks), there is no valid reason why such conditions may not also prevail in other groups of animals, either as a rule for the entire group, or as an exception for single individuals of a group where the conductivity follows the human type and not the bird's type.

Until now, as a rule, the explanation for the Wolff-Parkinson-White syndrome is to refer to the occasionally present bundle of Kent or to bundle branch acceleration, or to two interfering pacemakers.[3] It seems to be no less logical to suppose that occasionally in a human being a short cut of the stimulus conduction works by fibers of the conductive system, which reach certain subpericardial parts sooner than the normal conductive fibers reach the subendocardial muscle. Such a condition may be stable and work as a steady mechanism, or it may work transiently only and then produce a transient Wolff-Parkinson-White syndrome. Such an explanation of the syndrome would not need to

Received for publication June 12, 1950.

recur in each case, to the still unproved physiologic effect of a bundle of Kent and would be supported by the already proved conditions in certain groups of animals.

The experiments referred to in this paper were performed in the Laboratories of Fordham University, New York, Marine Biological Laboratory, Woods Hole, Mass., and Mount Sinai Hospital, New York. The assistance of each of these institutions is highly appreciated. The main facts were presented on April 19, 1950, at the fifty-ninth annual meeting of the American Physiological Society in Atlantic City, N. J.

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Clinical Reports

PAROXYSMAL AURICULAR TACHYCARDIA

Report of a Case With Persistent Ectopic Auricular Pacemaker, Without Sinoauricular Node Activity

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SINCE the earliest reports on paroxysmal auricular or supraventricular tachycardia by Bristow[1] in 1888 and by Bouveret[2] in 1889, considerable attention has been focused on the clinical significance and management of this disturbance of cardiac mechanism.[3-5] It is now known that this disturbance alone in the absence of any structural changes in the heart can produce heart failure and even death.

Of particular interest is the occasional occurrence of paroxysmal tachycardia in infants and young children. In 1941, Hubbard[6] added his series of nine cases to nineteen others in the literature reported within the first year of life. Six of his cases were observed during a single year. He also noted that paroxysmal tachycardia in infancy seems to follow a different course from that in older ages; for when it is adequately treated in infancy, it tends to disappear completely and not to recur even without constant medication. Moore,[7] in 1948, found sixteen others reported since Hubbard's series and added one unusual case of an infant who had thirty-one attacks of paroxysmal tachycardia between the ages of 8 days and 5½ months.

We are here reporting an additional case because of several interesting and unusual features. First, it is another typical example of the harmful effects of paroxysmal tachycardia alone. Second, it illustrates the value of digitalis in this condition. Finally, it is unique in that, although the tachycardia has been controlled, the cardiac mechanism still continues to be under the control of an ectopic auricular pacemaker. The interesting possibility of a nonfunctioning, an absent, or even a levoposed sinoauricular node is therefore suggested.

CASE REPORT

M. M. S., a 1 year and 11 months old girl, was admitted to the medical service of the Children's Hospital of Boston on Aug. 7, 1948, because of paroxysmis of rapid heart action of eight months duration.

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This study was supported in part by a grant from the Helen Hay Whitney Foundation.
Received for publication Feb. 9, 1950.

The child was well until the age of 15 months, at which time she had an episode of fever, tachycardia, and dyspnea. She was then hospitalized and was treated with penicillin and digitalis. That episode subsided, but since then she had had several similar attacks, accompanied by sweating and at times by abdominal pain and vomiting. These episodes varied in duration from one day to three weeks. Before coming to the Children's Hospital, she was hospitalized twice more, and in one of these episodes she was given quinidine without results. The liver was said to become enlarged during the attacks of tachycardia and dyspnea.

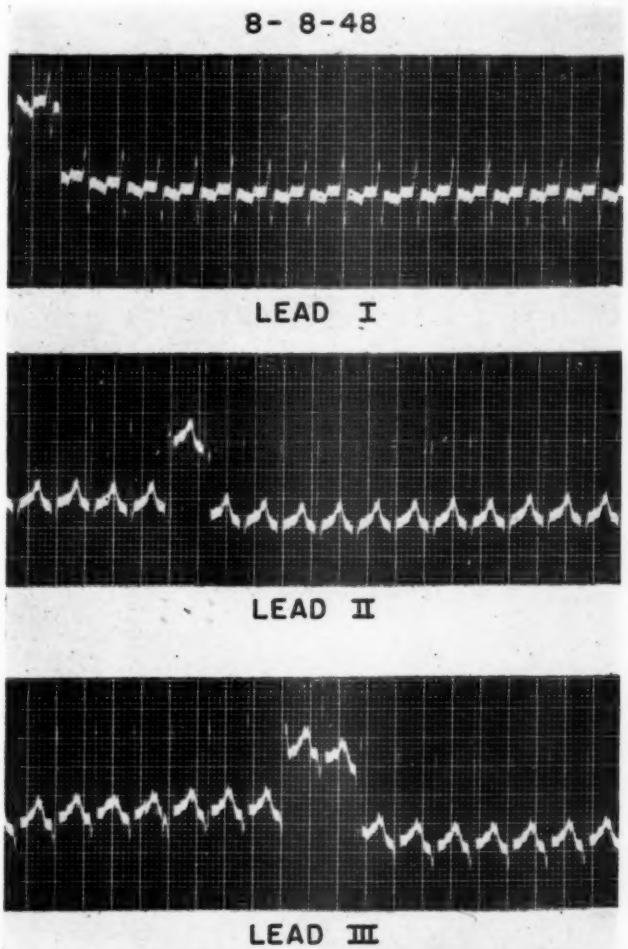
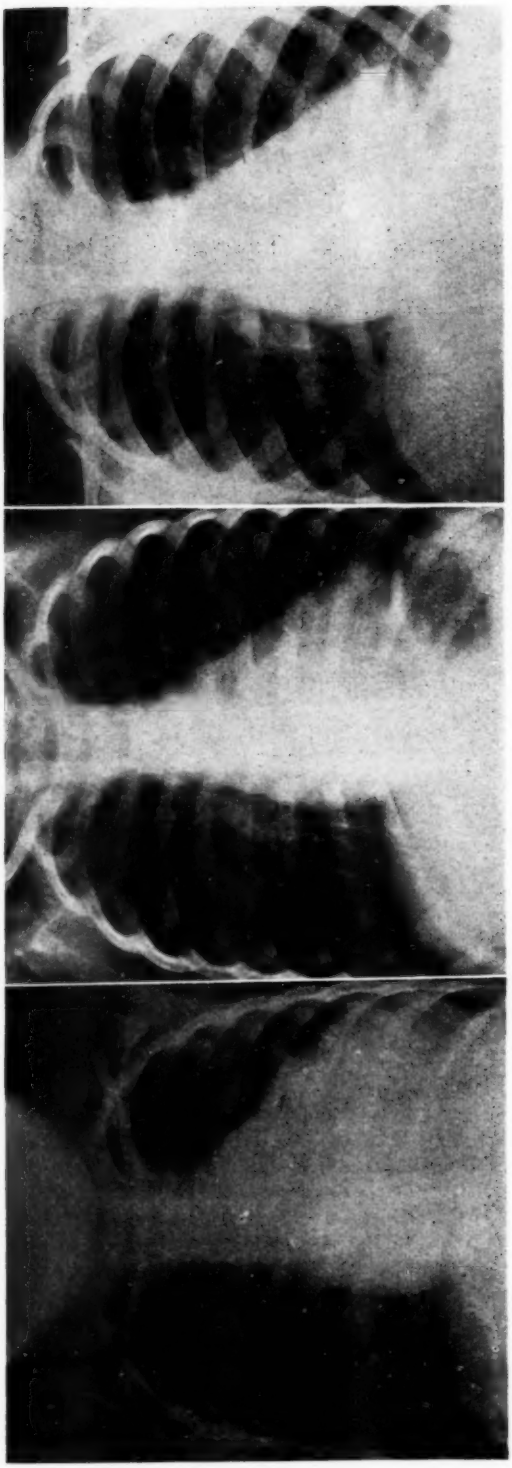


Fig. 1.—Standard limb leads taken on admission to the hospital and showing a supraventricular tachycardia. T and P waves are superimposed on each other.

The family history was noncontributory. She was born normally, though about a month prematurely. No cyanosis was noticed at birth, nor was an unusually rapid heart action noted. She was, however, placed in an incubator for twelve hours because of her birth weight of only 4 pounds, 12 ounces.

On admission she appeared to be well nourished and fairly well developed, weighing 24¾ pounds for a height of 92 cm. She looked chronically ill, moderately pale with a slightly cyanotic tinge on her lips. The anterior left side of the chest was slightly more prominent than the right.



A. B. C.

Fig. 2.—Posteroanterior roentgenograms showing marked cardiac enlargement in *A* (Sept. 9, 1948) and a heart size within normal limits for her age in *B* (Jan. 19, 1949) and in *C* (Dec. 10, 1949)

The left side of the heart was grossly enlarged with the point of maximum impulse 9 cm. from the midsternal line in the sixth left interspace. The cardiac rate was 210 per minute with a regular rhythm, normal sounds, and no murmur. The liver edge was felt 5 cm. below the right costal margin. No splenomegaly, ascites, or leg edema was noted. Femoral and dorsalis pedis pulsations were normal. The blood pressure in the arms by palpation was 114 mm. Hg systolic.

Her initial electrocardiogram (Fig. 1) revealed a supraventricular tachycardia, with a rate of 230 per minute, normal QRS complexes, and superimposed T and P waves. The x-ray examination (Fig. 2,*A*) showed a markedly enlarged heart in all its diameters predominantly toward the left. The auricles appeared to be enlarged proportionately to the rest of the heart.

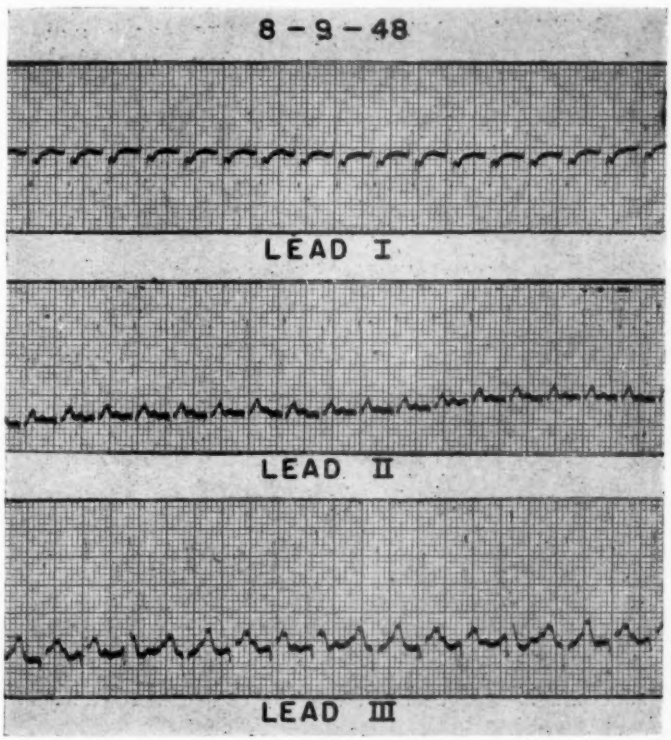


Fig. 3.—Standard limb leads on Sept. 9, 1948, showing normal rate for age, inverted P in Lead I, and prolonged P-R interval.

She was started on digitoxin with an initial dose of 0.2 mg., followed by 0.1 mg. after eight hours. The electrocardiogram (Fig. 3) then showed only a slight slowing of the heart rate. However, it was evident that digitalis had started its effect as shown by the prolongation of the P-R interval to a maximum of 0.20 second. Other tracings not reproduced here showed instances of Wenckebach phenomenon. At the same time it became clear from the inverted P waves in Lead I that the tachycardia was of an auricular type. She was then tried on Prostigmine with a single dose of 0.16 mg. on September 10 and two similar doses the next day. This produced no significant change in the ventricular rate and merely diminished the A-V block caused by digitalis.

Digitoxin was then resumed with an alternating daily dosage schedule of 0.1 mg. and 0.05 mg. Fig. 4 shows the gradual changes in her cardiac mechanism during this period. On September 13 she had a 3:2 A-V block, which became 2:1 block the next day. Finally, on September 15, she revealed for the first time a 1:1 auriculoventricular mechanism with a rate of 100 per minute. Nevertheless, in spite of this normal rate and auriculoventricular relationship, the pacemaker

remained an ectopic auricular focus as indicated by the negative P waves in Lead I. Although the roentgenograms did not suggest dextrocardia, further study of this possibility from the electrocardiographic point of view was made. In Fig. 5, the electrocardiogram, with unipolar limb and chest leads, corroborated the x-ray findings of a normally placed heart. The striking abnormality was in the P waves, which were deeply inverted in Leads I and aV_L, diphasic in aV_R and $V_{4,6}$, and upright in $V_{1,2}$.

A further attempt to disclose sinoauricular node activity was made through a trial on quinidine with the hope of depressing the ectopic auricular focus. After a test dose of 25 mg., the patient was given a series of four doses of 50 mg. of quinidine sulfate at intervals of three hours.

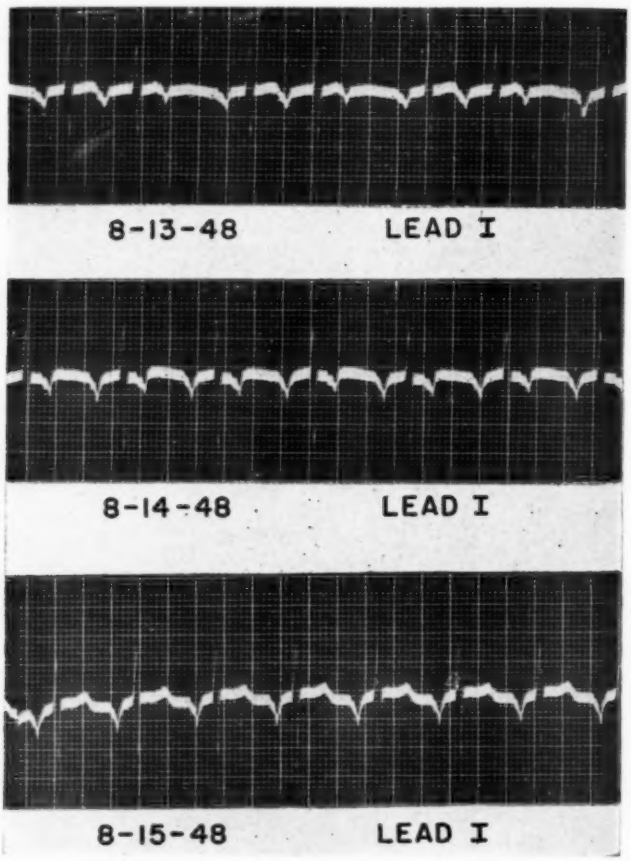


Fig. 4.—Lead I electrocardiograms on three successive days while the patient was under digitoxin, showing changes in cardiac mechanism from 3:2 A-V block to 2:1 to 1:1 auriculoventricular mechanism. In all the P wave is deeply inverted.

This trial, like the one she had had previously at another hospital, failed to influence the ectopic pacemaker. She was, therefore, continued on digitoxin at the same alternating daily doses previously mentioned. Apparently digitalis was the only agent capable of keeping the ectopic pacemaker from unusually rapid activity. In fact, several observations were made in which the patient's cardiac rate was reduced to 88 per minute. In all instances, however, the electrocardiogram persisted in showing an ectopic auricular pacemaker. There never was a single cardiac cycle with an upright P wave in Lead I.

The child gradually recovered from her tachycardia and congestive failure. As the rate slowed, a faint systolic murmur became audible over the apex. On the thirty-second hospital day she was discharged with her cardiac rate ranging between 90 and 110 per minute, a smaller

heart and liver, and a fairly healthy appearance. It was advised to continue the same digitalis schedule. Her roentgenogram on Jan. 19, 1949, (Fig. 2,*B*) revealed the heart within normal limits for her age.

A year later, on Sept. 8, 1949, the patient was brought back for a routine checkup. Since hospital discharge she had had two episodes of mild upper respiratory infection. In one of them her heart rate was 140 per minute, but she had not developed dyspnea nor congestive failure. She now appeared well with good development and a heart that was essentially normal. Her heart rate still ranged between 90 and 110 per minute, and the apical systolic murmur was even fainter than before. The liver edge could not be felt. Her electrocardiogram was identical with that on discharge from the hospital and showed essentially the same features as those shown in Fig. 4. Throughout this period she had been taking digitoxin as originally prescribed. In a year's period, therefore, there had been no instance where the P wave in Lead I was found to be upright and thus no evidence of sinoauricular node activity in spite of her normal heart rate. Her latest x-ray taken Dec. 10, 1949, (Fig. 2,*C*) showed the same normal findings as those taken shortly after her discharge from the hospital.

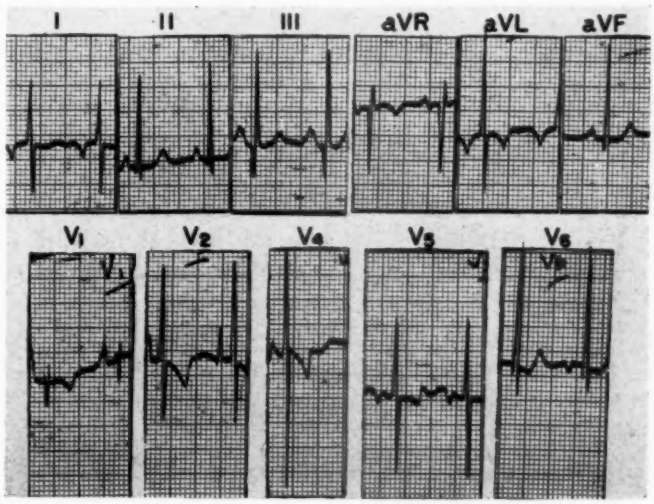


Fig. 5.—**Complete electrocardiographic study, standard and unipolar limb leads, and unipolar chest leads, showing no evidence of dextrocardia but definite abnormalities in the P waves.**

DISCUSSION

There seems to be no doubt that the cause of congestive failure in this child was the tachycardia itself. It is well accepted that tachycardia alone can precipitate heart failure with marked cardiac dilatation, which may be acute and even fatal. In fact, it is perhaps unusual to find no cardiac hypertrophy nor myocardial insufficiency in prolonged and severe paroxysms of tachycardia as was reported in two cases by Weiss and McGuire.[8]

The possibilities of congenital heart disease and nonspecific myocarditis were considered in this case. However, the fact that the patient's cardiac status returned to normal as the tachycardia was controlled and that all her previous episodes were distinctly related to her paroxysms of tachycardia suggests that the underlying mechanism of the entire clinical picture was the tachycardia itself. Even her fever could have been an associated manifestation of the con-

gestive failure. In 1940, Kinney and White[9] reviewed 200 cases of congestive failure and noted that all except four had fever. In the present case, the patient's temperature in the hospital oscillated between 98° and 101° F. without any clear evidence of infection. Her leucocyte count was only 8,300 per cubic millimeter with a normal differential. Her course subsequent to hospital discharge confirmed the impression that the main disturbance of cardiac function was the tachycardia and that there is probably no underlying organic heart disease except for the possibility that the pacemaker is congenitally mal-located or absent.

The unique feature of this case is the fact that there is no electrocardiographic evidence of sinoauricular node activity even after the control of the tachycardia and even with a heart rate as slow as 88 per minute with a 1:1 auriculoventricular relationship. The P wave was and still remains after a year deeply inverted in Leads I and aV_L, diphasic in aV_R and V_{4-6} and upright in $V_{1,2}$, all of which indicate that the pacemaker is an ectopic auricular focus somewhere in the left auricle.

In Hubbard's series, two cases showed transitory inversion of the P waves in Lead I immediately following the control of the tachycardia. These two cases were instances of instability of the pacemaker. Thus, the P waves varied from negative to upright as the pacemaker wandered from ectopic auricular foci to the sinoauricular node. It was evident, then, that the sinoauricular node was present, normally situated, and active even during such transition periods. In contrast, electrocardiograms in our case never showed and still do not reveal a single upright P wave in Lead I even at perfectly normal rates. It can be said, therefore, that the normal pacemaker in this case is an ectopic auricular focus. Is there no sinoauricular node? Is it a case of a nonfunctioning sinoauricular node with a substitute ectopic auricular pacemaker? Or is it a levoposed sinoauricular node?

In a normally placed heart, a negative P wave in Lead I, without shortening of the P-R interval, would indicate that the source of the impulse is an ectopic focus somewhere in the left auricle. Abramson, Fenichel, and Shookhoff[10] studied electrical activity in the auricles by stimulating various sites of both auricles. They obtained a negative P wave in Lead I only when they stimulated the left auricle. For this same reason in dextrocardia the normal P wave appears to be negative in Lead I because of the reversed relationships of the two auricles and the consequent proximity of the sinus node to the left arm. As a result, the travel of depolarization in the auricles is also reversed; that is, from left to right instead of from right to left as normally occurs. Abnormalities of the P wave have been studied in various diseases,[11,12] including atrial infarction,[13,14] and in no instance was an inverted P wave in Lead I observed. On the other hand, there is no case in the literature where the sinoauricular node was found to be in the left auricle instead of in its normal location in the right auricle. This possibility is considered because of the persistence of the ectopic auricular pacemaker in this case even at normal rates without any sign of an active, normally placed sinoauricular node. Whichever of these possibilities becomes eventually proved, this case will remain very unusual and possibly unique.

Finally, the apparent ineffectiveness of quinidine and Prostigmine and the proved efficacy of digitalis are of practical interest. In Moore's unusual case, he felt that quinidine and acetyl-beta-methylcholine were more effective than digitalis; while Landtman and Mannheimer obtained good results with Prostigmine. On the other hand, Hubbard found digitalis most efficient in his nine cases. Our present case, therefore, would seem to confirm Hubbard's experience. With the dose prescribed, digitalis effectively controlled the tachycardia without producing any sign of digitalis toxicity. That the control of the tachycardia was effected by this drug is further evidenced by the electrocardiographic signs of digitalis effect noticed; namely, the P-R prolongation and varying degrees of A-V block before the tachycardia finally subsided.

SUMMARY

An unusual case of a female child, 1 year and 11 months old, with paroxysmal auricular tachycardia is reported in which the cardiac mechanism persists in being an ectopic auricular pacemaker without any evidence of an active, normally placed sinoauricular node. A year after the control of the tachycardia, her electrocardiogram still shows abnormalities in the P waves indicating an ectopic pacemaker somewhere in the left auricle.

This case illustrates again the harmful effects of tachycardia, namely, the producing of cardiac dilatation and congestive failure.

Digitalis was effective in controlling both the tachycardia and the congestive failure.

The authors are grateful to Dr. A. A. Rubin of Syracuse, N. Y., for supplying the roentgenograms in Fig. 2,*B*,*C*.

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ABERRANT ATRIOVENTRICULAR CONDUCTION WITH NORMAL P-R INTERVAL AND PROLONGED QRS COMPLEX SIMULATING BUNDLE BRANCH BLOCK

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ABERRANT atrioventricular conduction[1] (Wolff-Parkinson-White[2] syndrome) is usually characterized electrocardiographically by short P-R intervals and prolonged QRS complexes. However, variations of this pattern occur. Fox[1] and others have reported cases with short P-R intervals and abnormal but not prolonged QRS complexes. Also, it is suggested that QRS complexes of normal duration and without recognizable deformity, associated with short[3,4] or even normal[5] P-R intervals, may be produced by anomalous excitation of the ventricles.

The differentiation between QRS prolongation due to aberrant atrioventricular conduction and that due to intraventricular block is usually easy, the short P-R interval in the former being the principal though not the only distinguishing feature. Instances of aberrant atrioventricular conduction with P-R intervals of 0.12 second are on record[6-10] but are probably uncommon, for in two series totaling 106 patients,[10,11] the P-R interval exceeded 0.11 second in only four cases. Prolonged QRS complexes with P-R intervals longer than 0.12 second are generally considered diagnostic of intraventricular block. However, Öhnell[5] in 1944 reported five cases of aberrant atrioventricular conduction in which P-R intervals of 0.13 second or more were associated with prolonged QRS complexes; he stressed that these cases closely resembled instances of bundle branch block, but he did not record multiple precordial leads, by which a differentiation between the two conditions may often be made.[12] Wolff and White[10] referred to one case showing a P-R interval of 0.145 second during anomalous conduction; the electrocardiogram of this patient displayed both normal and abnormal QRS complexes. We know of only one other reported case[13] of this disorder showing prolonged QRS complexes and P-R intervals definitely more than 0.12 second.

We have studied a patient with aberrant atrioventricular conduction whose electrocardiogram closely resembled that of bundle branch block in that the P-R intervals were normal and the QRS complexes prolonged; furthermore, neither in standard nor precordial leads was the form of the QRS complexes typical of

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Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Received for publication Feb. 23, 1950.

aberrant atrioventricular conduction. The features which permit differentiation from bundle branch block are of interest.

CASE REPORT

A 33-year-old white laborer was admitted to Veterans Hospital on March 22, 1948, complaining of palpitation. In 1945, he began to have episodes of rapid, regular heart action coming on suddenly while he was in bed, ending while he slept. Such episodes recurred nightly for months and then ceased, but several months later paroxysms of rapid heart action, sudden in onset and cessation, began to occur frequently, especially on exertion, and were associated with slight breathlessness. The heart rate during these episodes was said to range between 100 and 204 beats per minute. There were no other symptoms. On Feb. 12, 1948, the patient entered a local hospital where hyperthyroidism was diagnosed (a report received later from that hospital stated that the basal metabolic rate was +39 per cent and that an electrocardiogram showed paroxysmal nodal tachycardia with a rate of 205 beats per minute). For five weeks prior to his admission to Veterans Hospital the patient received propylthiouracil and digitalis in amounts unknown to him.

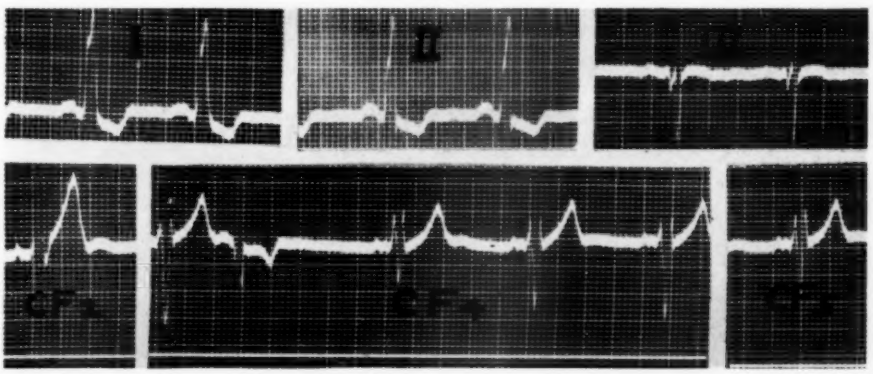

Fig. 1.—Electrocardiogram on fourth hospital day. P-R interval is 0.13 to 0.15 second in Lead I, 0.15 second in Lead II. QRS duration is 0.11 to 0.12 second in Leads I and II. Measurement in Lead III was difficult in this and all other tracings. The P waves are broad, QRS complexes deformed, T_1 and T_2 inverted, and ST_1 and ST_2 depressed. Note the supraventricular premature contraction in Lead CF_1 with QRS of normal duration, followed by QRS complexes which vary in form.

On physical examination the heart was of normal size, and the sounds were of good quality; there were no thrills or murmurs. Heart rate was 88 beats per minute, blood pressure 134/90 mm. Hg. Some premature contractions were heard, and there was one short burst of rapid, regular heart action. The right lobe of the thyroid gland was questionably enlarged. No other abnormalities were noted.

Routine laboratory studies were not remarkable. The basal metabolic rate on the fourth hospital day was −16 per cent; subsequent determinations were reported as −1, −3, +1 and −5 per cent, respectively. Circulation time studies gave normal results. Blood pressure ranged from 122 to 132 mm. Hg systolic and from 70 to 82 diastolic. Roentgenograms revealed an unusual prominence of the right cardiac border in the region of the right atrium, but no other abnormality was demonstrated on fluoroscopic examination or in angiocardiograms.

The patient received no medication except quinidine and atropine for diagnostic purposes. On a few occasions, premature contractions and paroxysms of tachycardia lasting for eight or ten beats were noted. The diagnosis of hyperthyroidism was not confirmed, and the patient was discharged May 8, 1948.

Many electrocardiograms were taken; the significant findings are illustrated. The initial electrocardiogram (Fig. 1) showed what appeared to be intraventricular block; the significance

of the supraventricular premature contraction with normal duration of QRS was not appreciated at the time. The normal P-R interval and prolonged QRS duration were not due to digitalis, since all subsequent tracings, including one on the twenty-ninth hospital day (Fig. 2), showed essentially the same features, though all electrocardiograms showed some variability in the form of the QRS complexes in the limb leads and especially in leads from the left side of the precordium.

Because of the history, aberrant atrioventricular conduction was suspected. An electrocardiogram following exercise showed no striking change from the control (Fig. 3); again, a supraventricular premature contraction with normal duration of QRS was recorded. The diagnosis of aberrant atrioventricular conduction was made when two episodes of paroxysmal tachycardia, during which the QRS complexes were of normal duration, were recorded (Fig. 4), and was confirmed by the effect of atropine on the electrocardiogram (Figs. 5,*A* and 5,*B*). Quinidine in moderate and large doses did not effect "normalization" (Fig. 5,*C*).

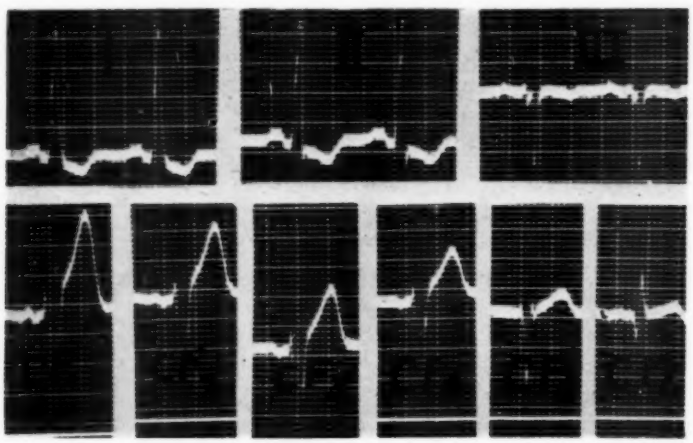

Fig. 2.—Electrocardiogram on twenty-ninth hospital day. P-R interval is 0.14 to 0.16 second. QRS duration 0.11 to 0.12 second. P waves are broad and notched. Note the change in form of QRS complexes in Leads I, II, CF_4 and CF_5 as compared with Fig. 1.

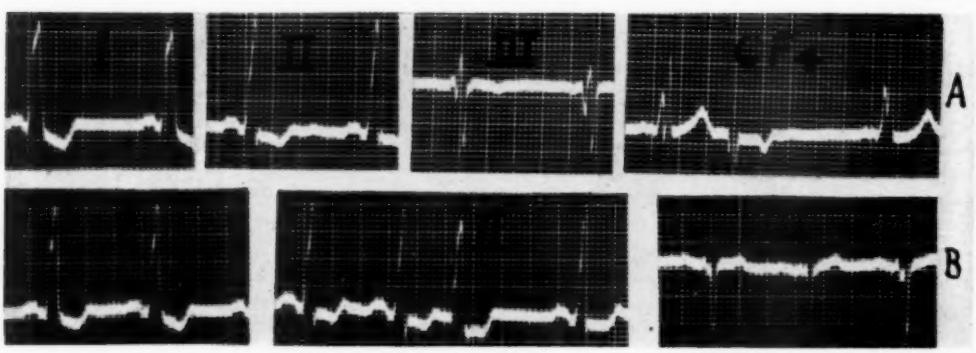

Fig. 3.—Electrocardiograms showing effect of exercise. *A*, Before exercise: P-R interval is longest in Lead II (0.16 second); QRS duration is 0.12 second. Complexes in Leads III and CF_4 are variable. There is a supraventricular premature contraction with QRS of normal duration in Lead CF_4. *B*, After exercise (patient hopped twenty-five times before each lead was taken): P-R interval is 0.16 second. QRS duration 0.11 to 0.12 second. Form of QRS complexes in Leads I and III has changed. A ventricular premature contraction followed by full compensatory pause is seen in Lead II.

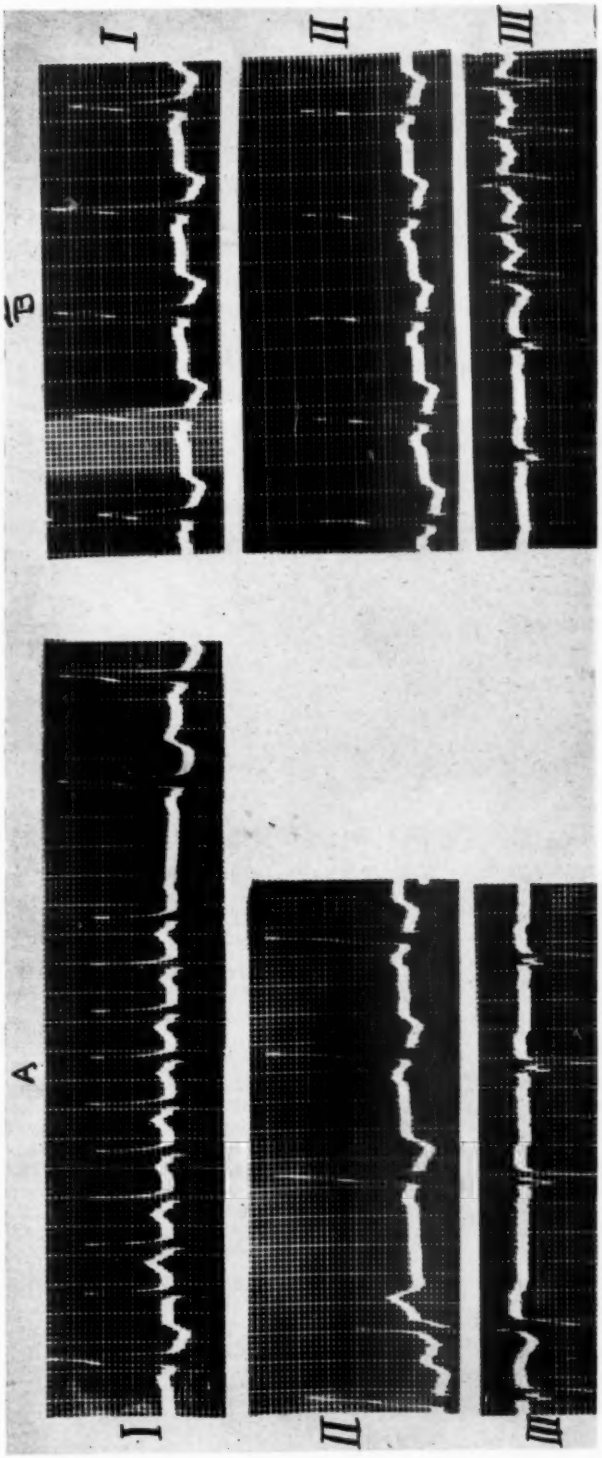

Fig. 4.—Electrocardiograms showing two episodes of supraventricular paroxysmal tachycardia. *A*, Paroxysm of nine beats at rate of 188 per minute is seen in Lead I, during which QRS duration is 0.08 second. In Leads II and III, the second complex is a supraventricular premature contraction. During sinus rhythm, P-R intervals vary even within each lead, and range from 0.12 to 0.15 second. QRS duration is 0.11 to 0.12 second. *B*, Paroxysm of tachycardia in Lead III, at rate of 180 per minute. Note variability of R_1. P-R interval ranges from 0.14 to 0.16 second. QRS duration is 0.11 to 0.12 second.

DISCUSSION

The electrocardiograms of this patient displayed two features unusual in aberrant atrioventricular conduction, viz., the length of the P-R interval and the form of the QRS complex.

The P-R interval varied in the different leads and sometimes even in successive complexes, but in Lead II was usually about 0.15 second. The beginning and end of the P wave and QRS complex in Lead III were seldom well delineated, but when reasonably accurate measurements in all limb leads could be made, the P-R interval, as determined by subtracting the longest QRS interval in any lead from the longest P-J interval in any lead,[14] was also about 0.15 second. The P waves were wide, and the P-R segment, which is usually shortened or absent during anomalous conduction, was well defined.

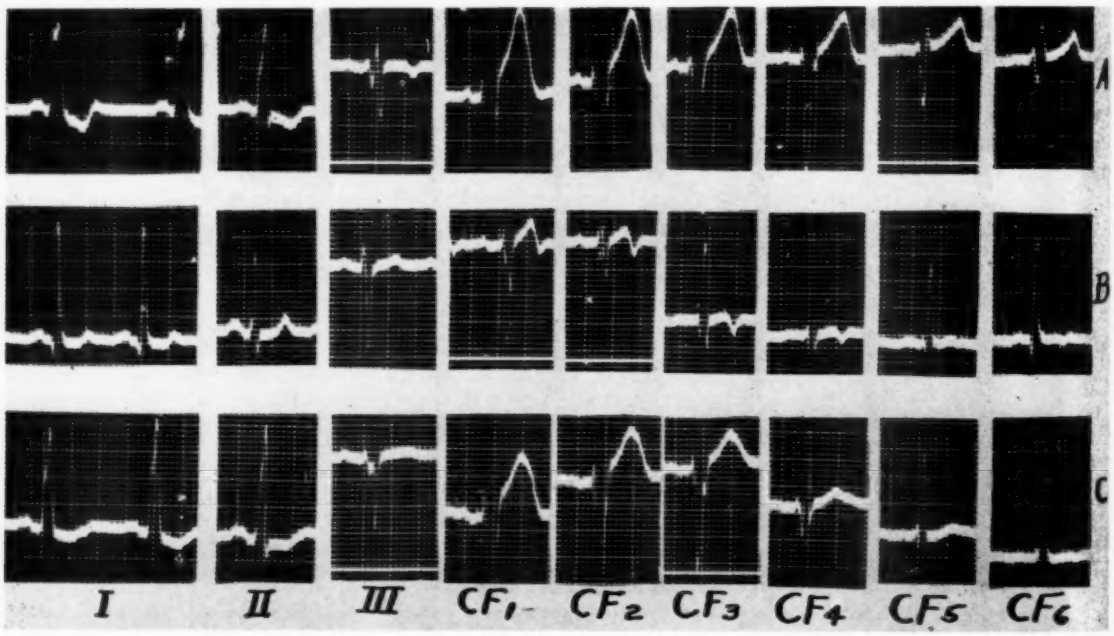

Fig. 5.—Electrocardiograms showing effect of atropine and of quinidine. *A*, Immediately before atropine. Rate is 65 per minute. In Lead II, P-R interval is 0.14 second, QRS duration 0.13 second. R_1 differs in form from that seen in previous tracings. *B*, Five minutes after intravenous administration of 0.002 Gm. atropine sulfate. Rate is 96 per minute. In Lead II, P-R interval is 0.16 second, QRS duration 0.08 second. There are marked QRS and T changes; T waves in precordial leads are abnormal. P_2 remains broad. Note the resemblance of ventricular complexes to those of supraventricular premature contractions in Figs. 1, 3,*A*, and 4,*A*. *C*, Three days later, following oral administration of 2.4 Gm. quinidine sulfate in course of six hours. QRS complexes remain widened.

In the limb leads the QRS complexes were somewhat variable in the different tracings and at times in a single tracing (e.g., in Lead I of Fig. 4,*B*), but their initial slope was usually steep and R_1 was slurred usually at or near the top of its ascending limb and occasionally on its descending limb. In contrast, QRS deflections in most cases of aberrant atrioventricular conduction have a gradual initial slope and are slurred mainly at their very onset[6,15,16]—contours which,

while typical, are by no means invariably found, for the shape of the first portion of the QRS complex may vary considerably[5] and the QRS deflection may be slurred throughout, or on its upstroke, or not at all.[3]

The literature contains little data on precordial lead findings in aberrant atrioventricular conduction. Rosenbaum and co-workers[15] found in Leads V_1, V_2, and V_E either of two patterns: one in which R was the sole or largest deflection, another in which S or QS was the chief QRS deflection in at least one of those leads. In leads from the left side of the precordium, the QRS complex was always dominated by a large R which was invariably slurred or notched at the base of its ascending limb; in Leads V_4 and V_5 there was usually a small S, while in V_6 the R was almost always smaller and S sometimes considerably deeper than in V_4 and V_5. Boyer[17] and Wolferth[12] agreed that the precordial electrocardiogram in aberrant atrioventricular conduction is very different from that of bundle branch block. Reed and co-workers[18] stated that slurring of the initial positive deflection of the QRS complexes in precordial leads is characteristic of aberrant atrioventricular conduction and is uncommon in cases of bundle branch block.

In the case presented, leads from the right side of the precordium showed one of the patterns described by Rosenbaum and co-workers,[15] but the QRS complexes in leads from the left side of the precordium, while very variable, were at no time typical of aberrant atrioventricular conduction.

The T waves in the limb leads in cases of aberrant atrioventricular conduction may be abnormal, but as a rule they approximate the normal.[16,19,20] In the present case, the T waves and ST segments in Leads I and II were markedly abnormal.

Despite these deviations, we believe this case is one of aberrant atrioventricular conduction. In true paroxysmal bundle branch block, which is usually a manifestation of advanced heart disease, the block is likely to appear when the ventricular rate is increased, whether by atropine or other means, and to disappear when the rate falls below a critical level;[21-25] in the present case the QRS interval became normal when the rate was increased by atropine or during episodes of paroxysmal tachycardia. There is no evidence that increased vagal tone can produce sustained inhibition of bundle branch conduction.[21] Atropine has no "normalizing" effect on the electrocardiogram of bundle branch block,[10] whereas it may convert the electrocardiographic pattern of aberrant atrioventricular conduction to normal.

In bundle branch block, an isolated beat showing a QRS interval within normal limits may appear under three circumstances: (1) If it is an escape beat,[26] or if it follows either a ventricular premature contraction[27,28] or a dropped ventricular beat.[22] The unblocked beat in such cases is preceded by a diastolic pause longer than usual, whereas in the present case the ectopic beats with normal QRS intervals were actually premature. (2) Rarely, if a ventricular premature beat originates in the septum.[29] In our patient, the premature beats with normal QRS intervals were supraventricular in origin. (3) Rarely, if a supraventricular premature beat is conducted rapidly during the supernormal phase. In aberrant atrioventricular conduction, supraventricular premature

beats frequently show normal QRS intervals, depending on the relation of the ectopic focus to the normal and anomalous conduction pathways.

Aberrant atrioventricular conduction is generally considered to be an innocuous condition, but Kimball and Burch[30] regard it as strongly suggestive or definite evidence of heart disease and advise a guarded prognosis. It has been pointed out[31] that the prolongation of ventricular systole and shortening of the period of diastolic rest resulting from intraventricular block diminish the heart's capacity for work and predispose it to fail, and we believe the same considerations apply in most cases of aberrant atrioventricular conduction. It is doubtful whether our patient has organic heart disease, but the unusual cardiac configuration in the roentgenogram and broad, notched P waves might be due to atrial disease, and the inverted T waves in precordial leads during normal conduction to ventricular disease. These T-wave changes were probably not due to atropine, since the ventricular complex in Lead CF_4 (Fig. 5,*B*) is similar to the spontaneously occurring supraventricular premature complexes (Figs. 1 and 3,*A*).

The broad P waves seen during both anomalous and normal conduction indicate slow depolarization of the atria, which might explain, at least in part, the length of the P-R interval during anomalous conduction and would suggest that during normal conduction the P-R interval would also be relatively long. Normal conduction was observed only following the administration of atropine; the P-R interval then was 0.16 second. Atropine increases conductivity through the atrioventricular node, so had a return to normal conduction occurred spontaneously, the P-R interval probably would have been longer. Furthermore, during aberrant atrioventricular conduction the P-J interval is usually the same as,[32] or occasionally shorter[10,33] but almost never longer* than it is during spontaneously occurring normal conduction. In this patient the P-J interval during anomalous conduction was usually 0.26 to 0.27 second, and if the QRS interval during normal conduction were to become 0.08 second (as it did with supraventricular premature contractions), the P-R interval would be 0.18 or 0.19 second or more. For these reasons we believe the P-R interval of 0.15 second during aberrant atrioventricular conduction, though not short by ordinary standards, was considerably shortened relative to the P-R interval during normal conduction. The patient of Wolff and White[10] who showed a P-R interval of 0.145 second during anomalous conduction, displayed a P-R interval of 0.212 second during normal conduction.

Obviously, it is neither necessary, practical, nor safe to employ such diagnostic tests as exercise, quinidine, or atropine in every case where the electrocardiogram is of the bundle branch block type; but whenever such an electrocardiogram is unexpectedly found in a patient who is not believed to have serious heart disease, aberrant atrioventricular conduction should be considered and cannot be excluded merely because the P-R interval is apparently normal.

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*Öhnell[5] states that the P-J interval during anomalous conduction is never longer than during normal conduction. Case 27 of Wolff and White[10] shows an exception to that rule.

SUMMARY AND CONCLUSIONS

1. A case of aberrant atrioventricular conduction is described in which the electrocardiogram simulated that of intraventricular block in that the P-R intervals appeared to be normal and the QRS complexes were prolonged. The form of the QRS complexes in the standard and precordial leads was not typical of aberrant atrioventricular conduction.

2. Aberrant atrioventricular conduction should be suspected when an electrocardiogram of bundle branch block type is an unexpected finding in a patient not believed to have serious heart disease.

3. The disappearance of the prolongation of QRS complexes during supraventricular premature contractions or during supraventricular paroxysmal tachycardia is evidence that bundle branch block does not exist.

4. In aberrant atrioventricular conduction the P-R interval may be shortened without being abnormally short.

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Notice

Research Grants and Fellowships

To be made available in 1951 by the Life Insurance Medical Research Fund

Applications for 1951 grants in aid of research on cardiovascular problems will be received by the Life Insurance Medical Research Fund up to Nov. 15, 1950. Support is available for physiological, biochemical, and other basic research which bears on cardiovascular problems, as well as for clinical investigation in this field. Preference is given to fundamental research. It is expected that about $550,000 will be awarded for these grants.

Applications for postdoctoral fellowships for training in research in 1951-1952 will also be received by this Fund up to Nov. 1, 1950. Preference is given to candidates who wish to work in the broad field of cardiovascular function or disease and to candidates who wish to work in institutions other than those in which they have obtained most of their experience. A doctor's degree (M.D. or Ph.D.) or the equivalent is required. The annual stipend varies, as a rule being between $3,000 and $4,000, with larger amounts in special cases. At least fifteen postdoctoral fellowships will be available.

New grants and fellowships will become available on July 1, 1951.

A number of predoctoral fellowships for basic training in research will also be awarded. Details are available on request.

Further information and application blanks may be secured from the Scientific Director, Life Insurance Medical Research Fund, 2 East 103rd Street, New York 29, New York.